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Diagnosis and Treatment of Invasive Mold Diseases

Sang-Oh Lee
Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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ABSTRACT

Although invasive fungal diseases are relatively less common than superficial diseases, there has been an overall increase in their incidence. Here, I review the epidemiology, diagnosis, and treatment of invasive mold diseases (IMDs) such as aspergillosis, mucormycosis, hyalohyphomycosis, and phaeohyphomycosis. Histopathologic demonstration of tissue invasion by hyphae or recovery of mold by the culture of a specimen obtained by a sterile procedure provides definitive evidence of IMD. If IMD cannot be confirmed through invasive procedures, IMD can be diagnosed through clinical criteria such as the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Instituteof Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) definitions. For initial primary therapy of invasive aspergillosis, voriconazole or isavuconazole is recommended and lipid formulations of amphotericin B are useful primary alternatives. Echinocandins are representative antifungal agents for salvage therapy. Treatment of invasive mucormycosis involves a combination of urgent surgical debridement of involved tissues and antifungal therapy. Lipid formulations of amphotericin B are the drug of choice for initial therapy. Isavuconazole or posaconazole can be used as salvage or step-down therapy. IMDs other than aspergillosis and mucormycosis include hyalohyphomycosis and phaeohyphomycosis, for which there is no standard therapy and the treatment depends on the clinical disease and status of the patient.

Keywords: Diagnosis; Treatment; Invasive fungal infections; Aspergillosis; Mucormycosis

INTRODUCTION

Invasive fungal diseases (IFDs) are generally distinguished from superficial fungal diseases based on the involvement of blood and other sterile sites or invasion into organ tissues. Although IFDs are relatively less common than superficial diseases, there has been an overall increase in the incidence of IFDs [1], partially due to increases in the number of immunocompromised patients receiving hematopoietic stem cell transplantation (HSCT), solid organ transplantation (SOT), or newer immunomodulatory agents. Fungal diseases are caused by yeast and mold. Candidiasis and cryptococcosis are representative IFDs caused by yeast. Here, I review the epidemiology, diagnosis, and treatment of invasive mold diseases (IMDs) such as aspergillosis, mucormycosis, hyalohyphomycosis, and phaeohyphomycosis.

EPIDEMIOLOGY

Recently, epidemiologic data of IFDs using healthcare network data in the United States were published [2]. The mean incidence of IFD was 27.2 cases/100,000

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Corresponding Author:
Sang-Oh Lee, MD, PhD
Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
Tel: +82-2-3010-3301, Fax: +82-2-3010-6970
Email: soleemd@amc.seoul.kr

patients per year, and the mean annual increase was 0.24 cases/100,000 patients. Candidiasis was the most common type (55.0%). Dimorphic fungi, primarily *Coccidioides* spp., comprised 25.1% of cases, followed by *Aspergillus* spp. (8.9%). According to the nationwide data from the National Health Insurance of Korea, the annual prevalence of fungal diseases increased from 6.9% in 2009 to 7.4% in 2013. Dermatophytosis, a representative superficial fungal disease, had the highest prevalence (5.2%), followed by IFDs (1.7%) such as cryptococcosis, aspergillosis, and mucormycosis [3]. In addition, cases of hyalohyphomycosis and phaeohyphomycosis, which are rare IMDs in patients with various underlying diseases, have been reported in Korea [4-6].

The proportion of each IFD varied depending on the patient category. In the Prospective Antifungal Therapy (PATH) Alliance registry data, invasive candidiasis was the major type of IFD in medical patients, non-transplant surgical patients, and those with solid tumors (79.8 - 90.7%), while invasive aspergillosis was more common in HSCT recipients and hematologic malignancy patients (35.2 - 49.5%). The 12-week survival rate for IFI varied based on the underlying condition, ranging from 37.5% for HSCT recipients to 77.5% for SOT recipients [7]. Invasive fungal pneumonia is a common and lethal complication in patients with hematologic malignancy [8]. As for IFDs that occurred after lung transplantation, candidiasis accounted for 52.2%, aspergillosis for 30.4%, and mucormycosis for 17.4% [9].

DIAGNOSIS OF IMDS

To confirm the diagnosis of IMDs, a specimen must be obtained by needle aspiration or biopsy. Histopathologic demonstration of tissue invasion by hyphae provides definitive evidence of IMD. Recovery of mold by the culture of a specimen obtained by a sterile procedure also provides a definite diagnosis of IMD. These categories are commonly refered to as "proven" IMDs [10]. However, needle aspiration or biopsy is often not feasible due to the risk of complications, especially in immunocompromised patients such as HSCT or SOT recipients and those with hematologic malignancy. In fact, in randomized controlled trials on IMD treatment, the proportions of proven cases ranged from just 1.8% to 27.0% [11-14]. In a Korean nationwide multicenter study for invasive pulmonary aspergillosis, only 8% were proven cases [15].

If IMD cannot be confirmed through invasive procedures, clinical criteria are used for diagnosis. In 2002, a consensus group of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) proposed standard definitions for IFDs for clinical and epidemiologic study [10]. Since then, these definitions have been widely used as clinical diagnostic criteria for IFDs, and were revised in 2008 and 2020 [16, 17]. The EORTC/MSG definitions consist of three elements: host factor, clinical criteria, and mycological criteria. If all three elements are satisfied, a diagnosis of "probable" IFDs can be made. If a case has the appropriate host factors and sufficient clinical evidence but no mycological support, it is diagnosed as "possible" IFDs. The possible category corresponds to empirical treatment at the clinician's discretion. Therefore, it is recommended to use antifungal agents carefully according to the opinions of the infectious disease experts.

1. Host factors

The EORTC/MSG definitions were originally created for use in patients with cancer and hematologic malignancy and HSCT recipients [10]. Therefore, in the 2002 EORTC/MSG definitions, host factors were mainly composed of neutropenia, persistent fever refractory to broad-spectrum antimicrobial treatment, graft-versus-host disease, and prolonged (>3 weeks) use of corticosteroids. In the 2008 revised definitions, various immunosuppressant treatments were also included to include SOT recipients [16]. The 2020 definitions listed more specific situations [17]. **Table 1** compares the 2008 and 2020 definitions and presents them in detail.

2. Clinical criteria

Clinical criteria of the 2002 EORTC/MSG definitions consisted of radiologic findings and clinical symptoms/signs [10]. For example, to diagnose pulmonary IMDs, chest CT findings required a halo sign, air-crescent sign, or cavity within the area of consolidation. Clinical symptoms/signs were coughs, chest pain, hemoptysis, dyspnea, and pleural rub. In the 2008 definitions, clinical symptoms/signs were excluded from clinical criteria because they were usually non-specific for the diagnosis of pulmonary IMDs [16]. In the 2008 definitions, radiologic findings were also revised; with only dense, well-circumscribed lesions, radiologic criteria for pulmonary IMDs were satisfied regardless of the presence of a halo sign (**Table 1**). It was because halo signs appear between the initial 7 - 10 days and might not be visible thereafter [18, 19].

There were some additional changes in the 2020 definitions [17]. Radiologic patterns of pulmonary IMDs were classified as either angio-invasive or airway-invasive forms [20, 21]. Angio-invasive forms, such as halo sign, air-crescent sign, and cavity within an infarct-shaped consolidation, were observed more often in neutropenic patients [22, 23]. Because the EORTC/MSG definitions were originally focused on patients with cancer and hematologic malignancy, radiologic patterns of angio-invasive form

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Table 1. Comparison of the 2008 and 2020 EORTC/MSG definitions for probable invasive pulmonary mold diseases

2008 [16]	2020 [17]
Host factors	**Host factors**
Recent history of neutropenia (<0.5 × 10^9 neutrophils/L [<500 neutrophils/mm^3] for >10 days) temporally related to the onset of fungal disease	Recent history of neutropenia (<0.5 × 10^9 neutrophils/L [<500 neutrophils/mm^3] for >10 days) temporally related to the onset of fungal disease
	Hematologic malignancy in receipt of treatment and in remission in the recent past
Receipt of an allogeneic stem cell transplant	Receipt of an allogeneic stem cell transplant
	Receipt of a solid organ transplant
Prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for ≥3 weeks	Prolonged use of corticosteroids at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days
Treatment with other recognized T-cell immunosuppressants, such as cyclosporine, TNF-α blockers, specific monoclonal antibodies, or nucleoside analogues during the past 90 days	Treatment with other recognized T cell immunosuppressants, such as calcineurin inhibitors, TNF-α blockers, lymphocyte-specific monoclonal antibodies, or immunosuppresive nucleoside analogues during the past 90 days
	Treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, *e.g.*, ibrutinib
Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency)	Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT 3 deficiency, or severe combined immunodeficiency)
	Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids
Clinical criteria	**Clinical criteria**
(Lower respiratory tract fungal disease)	(Pulmonary aspergillosis)
The presence of 1 of the following 3 signs on CT:	The presence of 1 of the following 4 patterns on CT:
- Dense, well-circumscribed lesions(s) with or without a halo sign	- Dense, well-circumscribed lesions(s) with or without a halo sign
- Air crescent sign	- Air crescent sign
- Cavity	- Cavity
	- Wedge-shaped and segmental or lobar consolidation
	(Other pulmonary mold diseases)
	- As for pulmonary aspergillosis but also including a reverse halo sign
Mycological criteria	**Mycological criteria**
(Direct test)	(Direct test)
Mold in sputum, bronchoalveolar lavage fluid, or bronchial brush, indicated by 1 of the following:	Any mold, for example, *Aspergillus*, *Fusarium*, *Scedosporium* species or Mucorales recovered by culture from sputum, BAL, bronchial brush, or aspirate
- Presence of fungal elements indicating a mold	
- Recovery by culture of a mold (*e.g.*, *Aspergillus*, *Fusarium*, Zygomycetes, or *Scedosporium* species)	Microscopical detection of fungal elements in sputum, BAL, bronchial brush, or aspirate indicating a mold
(Indirect test)	(Indirect test)
Galactomannan antigen detected in plasma, serum, or BAL fluid (Aspergillosis)	Galactomannan antigen in plasma, serum, or BAL (Aspergillosis)
	Any 1 of the following:
	- Single serum or plasma: ≥1.0
	- BAL fluid: ≥1.0
	- Single serum or plasma: ≥0.7 and BAL fluid ≥0.8
	Aspergillus PCR
	Any 1 of the following:
	- Plasma, serum, or whole blood 2 or more consecutive PCR tests positive
	- BAL fluid 2 or more duplicate PCR tests positive
	- At least 1 PCR test positive in plasma, serum, or whole blood and 1 PCR test positive in BAL fluid

EORTC/MSG, The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Instituteof Allergy and Infectious Diseases Mycoses Study Group; TNF, tumor necrosis factor; CT, computed tomography; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction.

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were mainly included even in the 2008 definitions. Airway-invasive forms, such as small airway lesions, peribronchial consolidations, and bronchiectasis, are often observed in non-neutropenic transplant patients [22, 23]. Based on the results of these studies, the findings of wedge-shaped and segmental or lobar consolidation were added to the 2020 definitions (**Table 1**).

The 2020 definitions were characterized by separating the clinical criteria for pulmonary aspergillosis and other pulmonary mold diseases (**Table 1**). The reverse halo sign was added as the clinical criteria for other pulmonary mold diseases such as mucormycosis. The reverse halo sign is more common in patients with pulmonary mucormycosis than in those with pulmonary aspergillosis [24]. The histology of the reverse halo sign includes an infarcted lung with a greater amount of hemorrhage in the peripheral solid ring than in the center ground-glass region [25].

While the clinical criteria of the EORTC/MSG definitions are presented by pulmonary diseases, tracheobronchitis, sinonasal diseases, and central nervous system infection, **Table 1** only summarizes pulmonary mold diseases, which are the most representative type.

3. Mycological criteria

According to the mycological criteria of the EORTC/MSG definitions, direct tests (*i.e.*, cytology, direct microscopy, or culture) or indirect tests (*i.e.*, detection of antigen or cell-wall constituents) can be used for the diagnosis of IMD (**Table 1**) [10, 16, 17]. If an appropriate specimen can be obtained, we can identify the presence of mold from the smear and culture, otherwise, indirect tests could be used. Galactomannan (GM) assay can be used for the diagnosis of aspergillosis, but there is no specific test for other mold diseases.

In experimental assays, the detection of *Aspergillus* antigenemia seems to correlate with clinical diagnosis and treatment response of antifungal therapy in invasive aspergillosis [26, 27]. A sandwich ELISA technique that uses a monoclonal antibody to GM has been developed [28]. The GM assay (Platelia *Aspergillus*, Bio-Rad, Hercules, CA, USA) could be applied to cerebrospinal fluid and bronchoalveolar lavage fluid as well as plasma and serum [16]. The GM assay is performed with an optical read-out that is interpreted as a ratio relative to the optical density (OD) of a threshold control provided by the manufacturer; this ratio is called the OD index. The cut-off index for the GM assay was originally set at 1.0 - 1.5 in order to minimize false-positive results [10], but it was lowered to 0.5 in the 2008 EORTC/MSG definitions [16]. The lowered cut-off value improved the overall performance of the test for adult hematology patients [29]. In the 2020 EORTC/MSG definitions, however, the cut-off index has been raised again (1.0 in serum, plasma, or bronchoalveolar lavage fluid) in order to ensure a higher likelihood of diagnostic certainty for clinical trial purposes (**Table 1**) [17, 30].

The determination of (1,3)-β-d-glucan (BDG) serum levels is a noninvasive test for circulating fungal cell wall components. The BDG assay is not specific for *Aspergillus* species and can produce positive results in patients with a variety of IFDs, including candidiasis and *Pneumocystis jirovecii*. However, it is typically negative in patients with mucormycosis or cryptococcosis [31, 32]. There are several different commercial assays available in different countries. A commercial BDG assay (Fungitell assay, Associates of Cape Cod, East Falmouth, MA, USA) has been approved by the FDA. However, BDG was not considered to provide mycological evidence of any IMD [17] since BDG detection is not specific to a single IMD.

In the 2008 EORTC/MSG definitions, molecular methods of detecting fungi in clinical specimens (*e.g.*, polymerase chain reaction [PCR]) were not included in the definitions because there was as yet to be a standard, and none of the techniques had been clinically validated [16]. Since then, much progress has been made in PCR assays for *Aspergillus*. In a meta-analysis of 25 studies, the sensitivity and specificity of PCR to detect invasive aspergillosis were 84.0% and 76.0%, respectively. When at least two PCR results were positive, the sensitivity was 64.0% and the specificity was 95.0% [33]. Many other meta-analyses showed similar results. Standardized protocols for nucleic acid extraction, sample types, volumes, and processing have been developed by the European Aspergillus PCR Initiative/Fungal PCR Initiative [34]. As a result of these efforts, 2 or more consecutive positive results of *Aspergillus* PCR was included in the mycological criteria of the 2020 EORTC/MSG definitions (**Table 1**) [17].

4. Diagnostic criteria for other host groups

In recent years, there has been an increasing number of reports of IMDs accompanying various infectious diseases. Invasive pulmonary aspergillosis can develop in patients admitted to intensive care units due to severe influenza or severe fever with thrombocytopenia syndrome [35-37]. The category of proven IMD can apply to any patient, regardless of whether the patient is immunocompromised. However, probable IMD requires the presence of at least 1 host factor, clinical and mycological criteria, and is proposed for immunocompromised patients only [16, 17]. As severe influenza or severe fever with thrombocytopenia syndrome are not a host factor for IMD, efforts to create new diagnostic algorithms are ongoing [36, 38, 39]. In the coronavirus disease 2019 (COVID-19) pandemic situation, many cases of coronavirus disease-associated pulmonary aspergillosis (CAPA) were reported [40, 41]. In order to diagnose CAPA in patients

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with COVID-19, diagnostic criteria are being created by applying criteria for influenza-associated pulmonary aspergillosis (IAPA) and the EORTC/MSG definitions [42].

TREATMENT OF INVASIVE ASPERGILLOSIS

1. Initial therapy for invasive aspergillosis

For initial primary therapy of invasive aspergillosis, voriconazole is recommended (**Table 2**) [43-45]. Even in the early 2000s, conventional amphotericin B deoxycholate was the standard therapy for invasive aspergillosis, although responses were suboptimal (less than 40.0%) and it had multiple adverse effects [46]. Voriconazole gained its current status based on a randomized, unblinded trial published in 2002 [47] that compared 144 patients in the voriconazole group and 133 patients in the amphotericin B group with definite or probable aspergillosis. This trial reported that compared with amphotericin B, initial therapy with voriconazole led to better responses (successful outcome at week 12, 52.8% *vs.* 31.6%) and a better survival rate at 12 weeks (70.8% *vs.* 57.9%) while resulting in fewer severe side effects such as nephrotoxicity.

During voriconazole therapy, therapeutic drug monitoring (TDM) is recommended [43-45]. The target trough level of

Table 2. Antifungal treatment of invasive aspergillosis

Agents	Dose	Recommendation	Adverse events	Additional consideration	Monitoring
Voriconazole	6 mg/kg IV/PO[a] every 12 h for 1 d, followed by 4 mg/kg IV/PO every 12 h	Primary [43-45]	Hepatotoxicity Visual disturbance Audio or visual hallucination Rash and photosensitivity	High CNS penetration Not in urine in active form Numerous drug interactions	Liver function test TDM, target trough level 1 - 5.5 mg/L
Isavuconazole	200 mg IV/PO[a] every 8 h for 6 doses, followed by 200 mg IV/PO once daily	Primary [45] Primary alternative [43, 44]	Hepatotoxicity[b] Visual disturbance[b] Audio or visual hallucination[c] Rash[b]	No dose adjustment for renal and hepatic impairment High CNS penetration (animal model) Not in urine in active form Numerous drug interaction	Liver function test TDM is not routinely recommended[d]
Liposomal amphotericin B	3 - 5 mg/kg/d IV	Primary alternative [43-45]	Nephrotoxicity Electrolyte abnormalities Acute infusion related reactions[e]		Renal function test Electrolytes
Caspofungin	70 mg IV on day 1 and 50 mg IV/d thereafter	Salvage [43-45]		No dose adjustment for renal impairment No drug in CSF or urine	Liver function test
Anidulafungin	200 mg IV on day 1 and 100 mg IV daily thereafter	Salvage [43]		No dose adjustment for renal and hepatic impairment No drug in CSF or urine	
Micafungin	100 - 150 mg IV daily	Salvage [43-45]		No dose adjustment for renal impairment No drug in CSF or urine	Liver function test
Posaconazole	300 mg PO (tablets)/IV twice daily on day 1 followed by 300 mg PO (tablets)/IV once daily on day 2 and thereafter When using suspension 200 mg PO every 8 h or 400 mg PO every 12 h	Salvage [43-45]	Hepatotoxicity	No dose adjustment for renal impairment Low CNS penetration Not in urine in active form Numerous drug interaction	Liver function test TDM, target trough level >1 mg/L (preferably >1.25 mg/L)

[a]IV loading favored in patients with CNS infection, bulky disease, and multifocal infection.
[b]Less frequent than voriconazole.
[c]Similar frequency between isavuconazole and voriconazole.
[d]TDM is not routinely recommended because there is not a clear exposure-response relationship and low variability of plasma level.
[e]Fever, chills or rigors, dyspnea, hypotension, tachycardia, hypertension, hypoxia, and chest pain (immediate hypersensitivity reaction).
IV, intravenous; PO, oral; CNS, central nervous system; CSF, cerebrospinal fluid; TDM, therapeutic drug monitoring.

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voriconazole is 1 - 5.5 mg/L. Routine TDM of voriconazole may reduce the incidence of drug discontinuation due to adverse events and improve the treatment response [48]. Considering that voriconazole interacts with various drugs such as cyclosporine, tacrolimus, and sirolimus, TDM of potentially interacting drugs is also needed. Elevation of hepatic enzymes is the most common adverse event of voriconazole, followed by hallucination and visual disturbance [48].

Isavuconazole is the primary or primary alternative drug for the treatment of invasive aspergillosis [43-45]. In phase 3, randomized-controlled trial, isavuconazole was non-inferior to voriconazole for the primary therapy of IMDs including invasive aspergillosis [12]. In the isavuconazole group of this trial, hepatotoxicity, visual disturbance, and rash were less common than in the voriconazole group. However, the incidence of audio or visual hallucinations was similar between the two groups. TDM of isavuconazole is not routinely recommended because there is no clear exposure-response relationship and low variability of plasma level [49].

Recently, a phase 3, randomized-controlled trial assessed the non-inferiority of posaconazole to voriconazole for the primary therapy of invasive aspergillosis [13]. In this trial, posaconazole was non-inferior to voriconazole for all-cause mortality until day 42 and had fewer adverse events than voriconazole. Although posaconazole is recommended as salvage therapy in the recent international guidelines (**Table 2**) [43-45], it might be included as primary therapy in the next revision of the guidelines.

Liposomal amphotericin B or amphotericin B lipid complex are additional primary alternatives but these agents carry the risk of nephrotoxicity [43-45]. Although no randomized trial has been performed to evaluate the efficacy of these drugs compared with voriconazole as primary therapy, a series of randomized trials suggest their efficacy. A randomized trial evaluating the primary treatment of invasive aspergillosis using liposomal amphotericin B reported favorable outcomes, especially with regard to minimizing toxicities [50]. Lipid formulations of amphotericin B are useful as initial therapy for invasive aspergillosis in patients using drugs that interact with azoles. They are also useful for patients suspected of invasive aspergillosis and mucormycosis, but accurate diagnosis is difficult, especially in patients who have used prophylactic voriconazole for a long time.

2. Salvage therapy of invasive aspergillosis

Salvage therapy is a form of therapy given after a disease becomes refractory to or intolerant of primary therapy. If voriconazole or isavuconazole was used for primary therapy, lipid formulations of amphotericin B can be used as salvage therapy [44]. Representative antifungal agents for salvage therapy are echinocandins such as caspofungin, micafungin, and anidulafungin [43-45]. Caspofungin was approved as salvage therapy for invasive aspergillosis due to its high efficacy and acceptable safety [51]. In a study of 225 patients with invasive pulmonary aspergillosis, favorable responses were observed in 50.0% and 41.0% of patients treated with micafungin as primary or salvage therapy, respectively [52]. A unique attribute of anidulafungin is that it is eliminated by non-enzymatic degradation in the blood and does not require dosage adjustments in patients with renal or hepatic dysfunction [53].

Combination therapy for primary therapy of invasive aspergillosis is not routinely recommended, but it may be considered in a salvage situation. Because of their distinct mechanism of action, echinocandins have the potential for use in combination with antifungal agents with different mechanisms of action [14, 54]. Antifungal agent resistance due to antifungal abuse raised concern, and efforts for antifungal stewardship should not be neglected [55].

TREATMENT OF INVASIVE MUCORMYCOSIS

It is difficult to treat invasive mucormycosis with only antifungal agents because of its rapid progression and tissue destruction. Therefore, the treatment of invasive mucormycosis involves a combination of urgent surgical debridement of involved tissues and antifungal therapy [56]. In a retrospective study of invasive mucormycosis, characteristics such as single pulmonary involvement, no dissemination, and complete surgical removal of infected tissue were associated with decreased mortality [57]. Also early initiation of antifungal therapy improves the outcome of infection with mucormycosis [58].

There are no randomized trials that assessed the efficacy of antifungal agents for mucormycosis because it is rare. Lipid formulations of amphotericin B are the drug of choice for initial therapy. The usual starting dose is 5 mg/kg daily of liposomal amphotericin B or amphotericin B lipid complex, and it can be increased as high as 10 mg/kg daily in order to control the infection (**Table 3**) [56]. A small sized study enrolled 21 patients treated with isavuconazole as initial therapy, and compared the results to 33 matched patients treated with amphotericin B formulations from the FungiScope registry and showed that isavuconazole had similar efficacy to that of amphotericin B formulations [59]. As a result, isavuconazole has been licensed in the USA for the initial therapy of mucormycosis. Many studies using posaconazole in the treatment of invasive mucormycosis are currently underway.

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Table 3. Antifungal treatment of invasive mucormycosis, hyalohyphomycosis, and phaeohyphomycosis

Invasive mold disease	Antifungal agent
Mucormycosis	Primary therapy Liposomal amphotericin B (5 - 10 mg/kg/d intravenous) Isavuconazole Surgical debridement of involved tissues and antifungal therapy Salvage therapy Isavuconazole Posaconazole
Hyalohyphomycosis	
Fusariosis	Primary therapy Voriconazole Liposomal amphotericin B
Scedosporiosis	Primary therapy Voriconazole
Pheohyphomycosis	No standard therapy Voriconazole, posaconazole, and itraconazole show the most consistent in vitro activity Liposomal amphotericin B is useful in some cases

Salvage therapy with isavuconazole was successful in clinical scenarios such as refractory disease, intolerance, or toxicity [59]. Posaconazole salvage therapy with oral suspension achieved a cure in two non-randomized clinical trials [60, 61]. For patients who have responded to a lipid formulation of amphotericin B, isavuconazole or posaconazole can be used for oral step-down therapy.

OTHER MOLD DISEASES

IMDs other than aspergillosis and mucormycosis are hyalohyphomycosis and phaeohyphomycosis [62]. In the past, the term "zygomycosis" was commonly used; however, the term "mucormycosis" is mainly used concurrently because the genera in the order Mucorales cause most cases of human infection [56]. Molds can be broadly divided into two morphologically distinct groups: those that produce septate hyphae and those that produce aseptate hyphae. Identification of aseptate hyphae in tissue is virtually pathognomonic of zygomycosis (mucormycosis). The discovery of septate hyphae in tissue is less diagnostic as septate hyphae may be caused by a vast number of species of molds. Septate molds are usually divided into those with pale or colorless (hyaline) hyphae (hyalohyphomycetes) and those with darkly pigmented hyphae (phaeohyphomycetes) [62].

1. Hyalohyphomycosis

Although infection due to *Aspergillus* spp. fits the description of colorless hyphae, aspergillosis is typically not included in hyalohyphomycosis, which includes various species such as *Fusarium*, *Scedosporium*, *Penicillium*, and *Acremonium* [62]. In patients with hematologic malignancy and HSCT recipients, almost all cases of fusariosis are disseminated at presentation [5, 63]. In contrast, fusariosis that occurs after SOT tends to be localized, and the outcome is better than in patients who have neutropenia [64]. Voriconazole or a lipid formulation of amphotericin B is recommended as primary therapy for invasive fusariosis (**Table 3**) [63].

Scedosporium spp. causes a wide spectrum of conditions, including mycetoma, colonization of the airway, sinopulmonary infections, extrapulmonary localized infections, and disseminated infections [65]. SOT from a nearly-drowned donor resulted in cases of fatal scedosporiosis [4]. As for primary therapy for invasive scedosporiosis, voriconazole is recommended together with surgical debridement when possible [63].

2. Phaeohyphomycosis

Phaeohyphomycosis is the result of infection with various species including *Alternaria*, *Exophiala*, *Dactylaria*, *Cladophialophora*, and *Curvularia* [62]. They cause a broad spectrum of diseases including skin and subcutaneous lesions, pneumonia, central nervous system disease, fungemia, and disseminated disease, particularly in immunocompromised patients. Extracutaneous invasive diseases can also occur in immunocompetent patients but are much less common. Skin and subcutaneous diseases were more common in SOT recipients, while pulmonary diseases were more common in HSCT recipients [66, 67].

There is no standard therapy for phaeohyphomycosis, and depends on the clinical disease and status of the patient. Surgical excision of the skin or subcutaneous lesion is often curative, although antifungal therapy is usually given in conjunction with surgery. Voriconazole, posaconazole, and itraconazole showed the most consistent in vitro

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activity against phaeohyphomycosis. Lipid formulations of amphotericin B have also been useful as an alternative therapy in some cases (**Table 3**). Combination antifungal therapy is recommended for cerebral abscesses when surgery is not possible and for disseminated infections in immunocompromised patients [66].

CONCLUSION

The EORTC/MSG definitions for the diagnosis of IMDs are not conclusive. In recent years, there has been an increasing number of reports of IMD cases accompanying various diseases. Therefore, the scope of host factors will continue to expand. In pulmonary IMDs, clinical criteria are mainly composed of radiologic findings, and there are many more things to be clarified in the future as reports on various radiologic findings are increasing depending on the type of underlying disease. Various indirect testing methods have been attempted for use in mycological criteria, and studies are needed to define their efficacy and appropriate cut-off values. Clinical studies on the treatment of IMDs are mainly conducted in invasive aspergillosis, and international joint studies should be performed to investigate the optimal therapeutic options for rarer IMDs such as mucormycosis, hyalohyphomycosis, and phaeohyphomycosis.

ORCID iDs
Sang-Oh Lee
https://orcid.org/0000-0003-1381-8787

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