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Advances in prophylaxis and treatment of invasive fungal infections: perspectives on hematologic diseases

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Abstract

Invasive fungal infections (IFIs) are common causes of mortality and morbidity in patients with hematologic diseases. Delayed initiation of antifungal treatment is related to mortality. *Aspergillus* sp. is the leading cause of IFI followed by *Candida* sp. Diagnosis is often challenging owing to variable conditions related to underlying diseases. Clinical suspect and prompt management is important. Imaging, biopsy, and non-culture-based tests must be considered together. New diagnostic procedures have been improved, including antigen-based assays and molecular detection of fungal DNA. Among hematologic diseases, patients with acute myeloid leukemia, myelodysplastic syndrome, recipients of hematopoietic stem cell transplantation are at high risk for IFIs. Antifungal prophylaxis is recommended for these high-risk patients. There are continuous attempts to achieve ideal management of IFIs. Scoring system for quality control has been developed with important recommendations of current guidelines. Higher adherence to guidelines is related to decreased mortality in IFIs.

Key Words Hematologic diseases, Invasive fungal infections, Diagnosis, Treatment, Quality control

INTRODUCTION

Fungal species are widely distributed in the environment and can cause opportunistic infections in immunocompromised hosts such as those with hematologic diseases. They can be classified according to their histologic forms: yeast (*Candida* sp.), mold (*Aspergillus*, *Rhizopus*), and dimorphic fungus. Clinical presentation of patients with fungal infections may range from mucocutaneous to deep organ infections [1, 2].

Recently, the incidence of invasive fungal infections (IFIs) has risen substantially and became a major problem in hospitals because of increased immunosuppressive therapy, organ and hematopoietic stem cell transplantation (HSCT), cytotoxic chemotherapy, invasive procedures and indwelling catheter [3, 4]. Patients with hematologic malignancies are at high risk of developing IFIs, which have high mortality and morbidity. Moreover, these group of patients are more exposed to antifungal agents which has contributed to diverse epidemiology and antifungal resistance [5-7].

Definitions for IFIs have been proposed (proven, probable, possible) to have a standard, shared definition, which may aid in communication between researchers, and ultimately improve diagnosis and management in clinical practice. Proven IFI is defined by the detection of fungus by histology or sterile tissue culture. Probable or possible IFI is defined depending on the setting or population, with respect to three elements: host factors, clinical features, and mycologic evidence [8].

IFIs caused by rare fungi are also increasing [9-11]. However, this article focused on IFIs, specifically invasive candidiasis, aspergillosis, and mucormycosis in patients with hematologic diseases. Furthermore, we also aimed to discuss the recent epidemiology, diagnosis, treatment, prophylaxis, and quality control in IFIs.

CANDIDIASIS

Candida species are commonly part of the normal flora, but they can cause a variety of opportunistic infections. Candidiasis is a broad term which refers to any infection caused by *Candida* sp. Invasive candidiasis refers to candide-

mia and deep-seated infection with or without candidemia. Examples of deep-seated infections include intra-abdominal abscess, peritonitis, osteomyelitis, brain abscess, endophthalmitis, and endocarditis.

Epidemiology

In patients with hematologic diseases, candidemia is the most common form of invasive candidiasis and is associated with high mortality rates up to 40% [12]. Neutropenia (neutrophil count <500 cells/μL) is a common risk factor and is usually related to cytotoxic chemotherapy or HSCT, use of broad-spectrum antibiotics gastrointestinal mucosal dysfunction, and indwelling vascular catheters [13]. Acute disseminated candidiasis or hepatosplenic candidiasis might also be seen in patients with prolonged neutropenia. Evidence of defining neutropenia as neutrophil count of less than 500 cells/μL followed previous study result [14].

At least 15 distinct *Candida* sp. can cause human diseases, but majority of invasive infections are caused by 5 species (*Candida albicans*, *Candida tropicalis*, *Candida glabrata*, *Candida krusei* and *Candida parapsilosis*). There is geographical, center-to-center variability in the prevalence of *Candida* species. Patient's predisposing factors and previous antifungal use also have a considerable influence on the distribution of *Candida* species. Candidiasis control should therefore include monitoring the epidemiology of *Candida* species and resistance to various antifungal agents [15, 16].

Traditionally, *C. albicans* has been the most common species but through the decades, non-albicans species have been increasing in proportion. We compared the epidemiology of candidemia from previous studies (Table 1). *C. glabrata* was the most common species among non-albicans species in Korea, similar in the United States [16-19]. *C. tropicalis* disputed this place in Asia-pacific region [20]. *C. tropicalis* followed *C. glabrata* in Korea.

In a single tertiary-care hospital in Korea where all data were collected from adult patients with hematologic diseases, the trend of decreasing *C. albicans* and increasing non-albicans species was the same. It was notable that *C. tropicalis* was considerably high in frequency and was already reported in several studies to be the most common non-albicans species causing candidemia in hematology patients [21-24]. *C. glabrata* recently increased from 9.5% to 24.6%, following the global trend. A main cause of the shift toward non-albicans species could be an increased azole resistance (ex. *C. glabrata*, *C. tropicalis*) due to the increased use of prophylactic antifungal agents. Furthermore, there is an increased use of echinocandin in patients with hematologic diseases for prophylaxis and/or empirical use [21] which could lead to epidemiological change.

Uncommon *Candida* species include *C. lusitaniae*, *C. guilliermondii*, and *C. auris*. Patients with hematologic diseases were at particular risk of *C. lusitaniae* and *C. guillermondii* [25]. These species are known to have intrinsic resistance to certain antifungal agent; *C. guilliermondii* resistant to echinocandins and *C. lusitaniae* resistant to amphotericin B. Therefore, selecting antifungal agent is challenging and accurate identification of these species is important [26-28]. *C. auris*, a nosocomial fungus, has become a serious threat for health care facilities around the globe. It can spread readily and has caused numerous healthcare-associated outbreaks. Moreover, most strains are resistant to at least one antifungal agent [29].

Diagnosis

Classic diagnostic methods for candidiasis are microscopy, histopathology and culture [15]. Tissue samples and body fluids from sterile sites must be collected aseptically and transported to the laboratory promptly. If it is candidemia, the preferred diagnostic would be blood culture [30]. Yeast isolation from normally sterile tissues or fluids is usually indicative of deep-seated infection; however, negative results do not exclude candidiasis. Identification of the isolate to species level is mandatory. Microscopy should make use of special stains such as Grocott-Gomori methenamine silver (GMS) and Periodic Acid Schiff (PAS). β-D-glucan (BDG)

Table 1. Changes of species distribution in the case of candidemia.

Pathogens	Seoul St. Mary's Hospital (adult hematology unit only)			Korea		United States		Asia	Europe[a]
Study period	2011–2021	2011–2016	2017–2021	2013	2021	2012	2019	2016	2011
References				[16]	[17]	[18]	[19]	[20]	[114]
Total	N=153 (%)	N=84 (%)	N=69 (%)	N=3,564 (%)	N=829 (%)	N=2,329 (%)	N=3,354 (%)	N=861 (%)	N=750 (%)
Candida albicans	38 (24.8)	27 (32.1)	11 (15.9)	1,354 (38.0)	353 (42.6)	877 (37.7)	1,307 (39.0)	309 (35.9)	(55.2)
Non-*C. albicans*	115 (75.1)	57 (67.9)	58 (84.1)	2,210 (62.0)	476 (57.4)	1,452 (62.3)	2,047 (61.0)	552 (64.1)	(44.8)
Candida tropicalis	55 (35.9)	30 (35.7)	25 (36.2)	557 (15.6)	156 (18.8)	241 (10.3)	292 (8.7)	264 (30.7)	(7.3)
Candida glabrata	25 (16.3)	8 (9.5)	17 (24.6)	589 (16.5)	159 (19.2)	670 (28.8)	949 (28.3)	116 (13.5)	(15.7)
Candida krusei	16 (10.5)	10 (11.9)	6 (8.7)	20 (0.6)	15 (1.8)	32 (1.4)	72 (2.1)	6 (0.7)	(2.5)
Candida parapsilosis	9 (5.9)	4 (4.8)	5 (7.2)	844 (23.7)	112 (13.5)	389 (16.7)	496 (14.8)	135 (15.7)	(13.7)
Candida lusitaniae	4 (2.6)	2 (2.4)	2 (2.9)	26 (0.7)	9 (1.1)	34 (1.5)	66 (2.0)	1 (0.1)	(1.2)
Candida auris					1 (0.1)				
Others	6 (3.9)	3 (3.6)	3 (4.3)	174 (4.9)	24 (2.9)	86 (3.7)	172 (5.1)	30 (3.5)	(2.6)

[a]Without exact number of cases, only percentage.

is a cell wall component of most fungi and is not specific to detect *Candida* species with high false positive rate. In contrast, BDG has high negative predictive value, suggesting that invasive candidiasis is unlikely when BDG is negative [15]. However, careful interpretation is needed as it may not be reliable in the early course of IFI. Immunohistochemistry, *in situ* hybridization, and polymerase chain reaction (PCR) based procedures are evaluated but utility and accuracy has not been warranted yet [31].

For patients with hematologic diseases, the possibility of obtaining samples of deep tissues is not warranted due to the patient's condition [32]. Therefore, many clinicians also rely on empirical evidence with prior exposure to antibacterial agents, existence of a central venous catheter (CVC), and recent abdominal surgery to establish diagnosis [15]. As the number of fungal infections has increased and as hosts have become more vulnerable, newer diagnostic tests are needed to identify the pathogens more quickly [33].

Breakthrough invasive candidiasis is also a problem in patients with hematologic diseases. Breakthrough infection is defined as an infection occurring in a patient receiving antifungal agents. Azole-resistant *Candida* sp., especially *C. krusei*, were major cause of breakthrough infection. Up to 45% had resistance to antifungal agent which the patient was receiving when the breakthrough infection occurred [34-36]. Therefore, changing antifungal agent to different class and testing susceptibility of cultured species are needed.

Chronic disseminated (hepatosplenic) candidiasis (CDC) is a unique clinical manifestation and almost seen in patients with hematologic diseases. CDC usually occur during recovery from neutropenia. Fever, right upper quadrant discomfort, nausea, elevate liver enzymes following recovery from neutropenia implicate CDC [37]. CT, MRI, or ultrasound imaging is helpful and small, peripheral, target-like abscesses are seen in the liver or spleen [31, 38].

Treatment

The mortality rate is closely correlated with delayed initiation of appropriate antifungal treatment. Therefore, prompt treatment is needed to improve prognostic outcomes in patients [39]. In candidemia, echinocandin antifungals are recommended as initial therapy. Transition from an echinocandin to fluconazole, usually within 5–7 days, is suggested in non-neutropenic patients who are clinically stable, have isolates that are susceptible to fluconazole, and have negative repeat blood cultures following treatment [40]. Fluconazole (intravenous or oral) is an acceptable alternative first line therapy if the patient is not critically ill and is unlikely to have a fluconazole-resistant *Candida* species [31]. However, antifungal resistance is an emerging problem worldwide and hematology patients might already be exposed to antifungal drugs for prophylaxis, complicating the selection of appropriate antifungal therapy [15]. For example, *C. glabrata* and *C. krusei* are more likely to have azole resistance and *C. parapsilosis* is known to have intrinsic resistance to echinocandin but not clinically significant [41].

Follow-up blood cultures should be performed every day or every other day to check when candidemia has been cleared. Recommended duration of therapy for candidemia without obvious metastatic complications is at least 2 weeks after the documented clearance of *Candida* species from the bloodstream, provided that neutropenia and other symptoms have resolved. For other complications such as endocarditis, surgical intervention and longer treatment are needed. Therefore, work up with transthoracic (TTE) or transesophageal (TEE) echocardiography should be done in patients with candidemia [32]. To check other disseminated focus, all non-neutropenic patients with candidemia should have a dilated ophthalmological examination within the first week after diagnosis to check for endophthalmitis. In neutropenic patients, ophthalmological findings are usually minimal until recovery from neutropenia; therefore, examination could be performed within the first week after recovery from neutropenia [31]. CVCs should be removed as early as possible when the source of candidemia is presumed to be the CVC. In neutropenic patients, sources of candidemia other than a CVC (ex. gastrointestinal tract) predominate. Removal of CVC should be considered on an individual basis [31, 42].

With CDC, therapy should be continued until lesions resolve on repeated imaging. The usual duration is several months and premature discontinuation of antifungal therapy can lead to relapse. If chemotherapy or HSCT is required, it may not be delayed because of the presence of chronic disseminated candidiasis [43].

For oropharyngeal candidiasis in patients with neutropenia, fluconazole 7–14 days is recommended. Chronic suppressive therapy is usually unnecessary. Esophageal candidiasis always requires systemic antifungal therapy. Diagnostic trial of antifungal therapy is available before endoscopic examination and intravenous therapy is recommended if the patient cannot tolerate oral therapy [31].

Echinocandin, a treatment of choice, has so-called sanctuary sites in the body such as eye, kidney, and meninges; therefore, it might be unsuitable for infection in those sites [44]. In addition, there is an increase in the resistance of *C. glabrata* to echinocandin [45]. In contrast, *C. parapsilosis* demonstrates innately higher minimum inhibitory concentrations (MICs) to echinocandins. If echinocandin or fluconazole is inadequate, liposomal amphotericin B could be an alternative.

ASPERGILLOSIS

Aspergillosis is the collective term used to describe all disease entities caused by any one of up to 50 pathogenic and allergenic species of *Aspergillus*. *Aspergillus* species continue to be an important cause of life-threatening infection in immunocompromised patients.

Epidemiology

In patients with hematologic diseases, *Aspergillus*-related infection is the most common IFI, followed by *Candida* in-

fections [46]. Incidence rates vary according to local epidemiology and many other factors, including environmental control. *Aspergillus fumigatus* complex is the most common species, followed by *A. flavus*, *A. niger*, and *A. terrus* [47]. Invasive aspergillosis (IA) is a severe IFI, which manifests mostly as invasive pulmonary aspergillosis (IPA). *A. fumigatus* is responsible for most cases of IA but more commonly colonizes the respiratory tract. In contrast, *A. flavus* and *A. niger* often colonize burn wounds, and *A. terreus* causes only invasive disease, and usually has a poor prognosis [1, 48-50]. Some species are known to have variable susceptibility to antifungal agents. *A. terreus* is infrequently susceptible to amphotericin B, whereas *A. calidoustus* and *A. lentulus* are resistant to multiple antifungal agents, including amphotericin B and voriconazole [50]. Azole resistance in *A. fumigatus* is also increasing [51], thus raising a problem.

Diagnosis

Diagnosis of IA remains difficult in many reasons. Both microscopy and culture should be attempted and tissue invasion by hyphae would provide a definitive diagnosis of IA. However, examinations such as tissue sampling may be difficult in hematology patients because of neutropenia and thrombocytopenia and yield of culture is frequently suboptimal [52]. Therefore, non-invasive diagnostic tests including non-culture-based tests have gained interest for improving diagnostic accuracy.

A high level of suspicion with meticulous physical examination is important since an immunocompromised patient may be relatively asymptomatic, interrupting early diagnosis

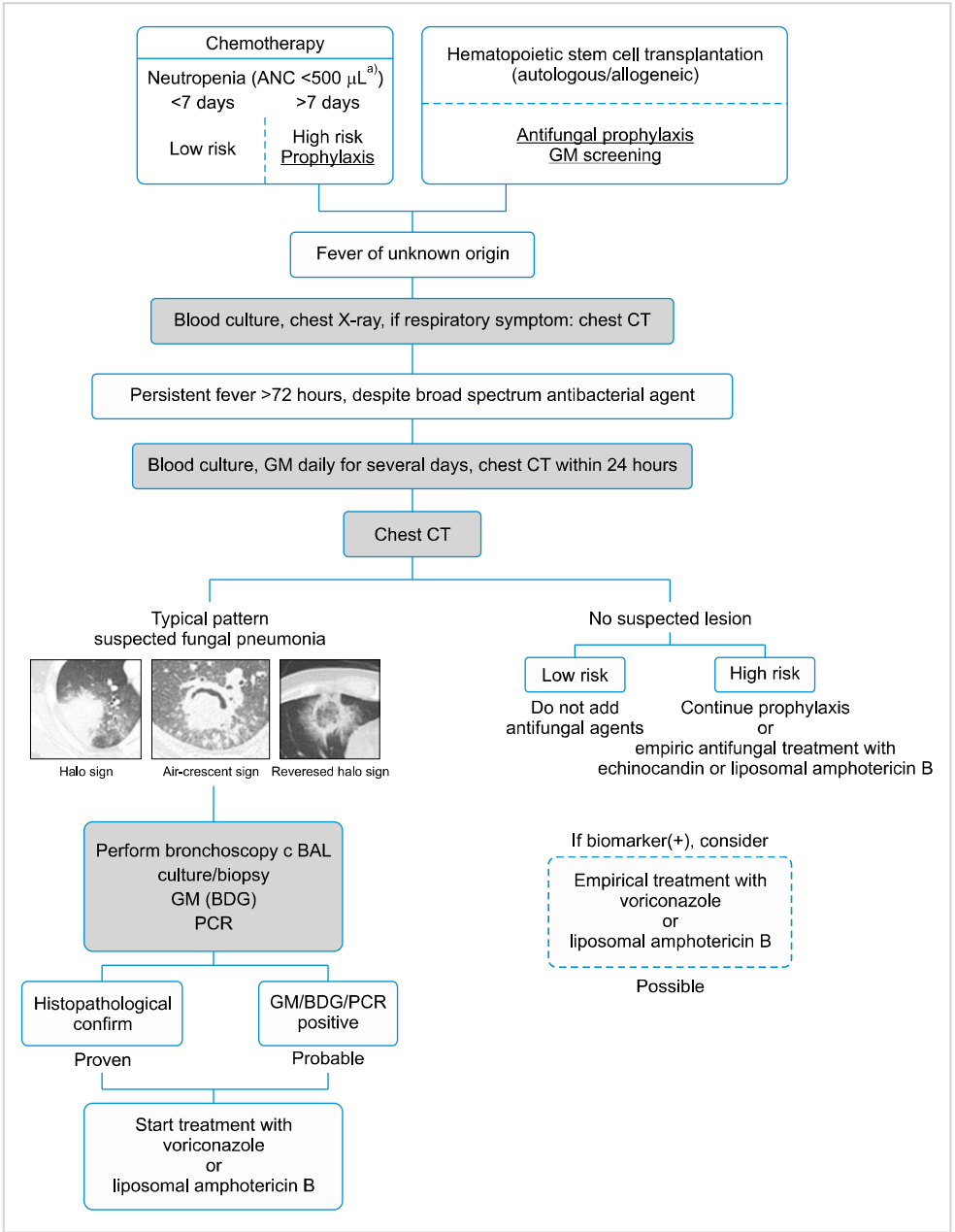

Fig. 1. Diagnosis of fungal pneumonia in patients with hematologic diseases. [a]Evidence of neutrophil count (<500 cells/μL) followed the guideline [14].
Abbreviations: ANC, absolute neutrophil count; BAL, bronchoalveolar lavage; BDG, (1→3) beta-D-glucan; CT, computed tomography; GM, galactomannan; PCR, polymerase chain reaction.

[50]. The most prevalent but unspecific sign of IPA reported in approximately 100% of patients is persistent fever despite treatment with broad-spectrum antibiotics [53]. Imaging is a critical component in the diagnosis, and CT scan is recommended whenever there is clinical suspicion or when the patients present with 72–96 hours of persistent neutropenic fever to find IPA or sinusitis regardless of simple chest radiograph results [54]. Routine contrast imaging is not recommended but could be considered if vessel involvement is suspected. Typical findings of IPA include consolidation with surrounding ground-glass opacity (halo sign) or cavitation [55]. Lung ultrasound (US) imaging has been considered as an alternative modality to diagnose invasive fungal pneumonia, including US-guided transthoracic needle aspiration. Considering it is a rapid, bedside, non-invasive technique, lung US could have a significant role but more study is required for expected accuracy [56-58].

Bronchoscopy with bronchoalveolar lavage (BAL) is recommended in patients in the suspicion of IPA. It seems to be a valuable diagnostic tool with high yield and low complication rate even in neutropenic patients with hematologic diseases. Therefore, regarding the diagnostic delay and impact on mortality, bronchoscopy with BAL should be considered if possible [59-61]. Routine fungal culture, cytology, and non-culture-based methods should be performed. Galactomannan (GM) detection is more sensitive than culture in the diagnosis of IA. Additionally, BAL fluid GM is more sensitive compared to serum GM in terms of diagnostic performance [62]. Serum assays for BDG with comparison to GM suggest higher sensitivity but are not a specific marker for *Aspergillus* and may produce frequent false positive results. Nucleic acid testing in clinical specimens such as PCR has become available and promising but still controversial due to the lack of conclusive validation [8]. Its negative predictive value is high but positive predictive value is low, therefore, conjunction with other diagnostic tests and clinical context is needed [63, 64]. If imaging findings implicate fungal infection with or without positive biomarkers (ex. GM, PCR), probable/possible IFI could be considered. As pulmonary infection is the most frequent form of IFIs in patients with hematologic diseases, we depicted the diagnostic process of invasive fungal pneumonia as an example (Fig. 1).

Treatment

For suspected IA, current guideline recommends voriconazole or isavuconazole as the treatment of choice. Isavuconazole is a mold-active triazole antifungal agent and is also susceptible to other molds including mucormycosis. Therefore, isavuconazole could be considered when co-infection of IA with other molds cannot be excluded [65]. If contraindicated or not tolerated, liposomal amphotericin B may be considered as an alternative. Amphotericin B deoxycholate is no longer a primary option but can be used in limited settings when no other antifungal agents are available [66]. Itraconazole should not be used as first line therapy although it is a potential option due to drug-drug interactions. Echinocandin also is not recommended because outcomes were not favorable with monotherapy [67]. Treatment should be continued for a minimum of 6–12 weeks, largely dependent on the degree and duration of immunosuppression, sites of infection, and evidence of disease improvement. Higher GM level is known as a risk factor related to mortality and follow up can be used to monitor disease progression or therapeutic response [68].

When persistent fever exists but no infiltrate seen in chest imaging, possible focus other than the lung should be considered. If there are no suspected focus and biologic markers such as GM, and PCR is negative, no empirical treatment would be required. However, in patients under mold-active prophylaxis, therapeutic drug monitoring (TDM) for prophylactic azoles such as posaconazole and voriconazole should be done and breakthrough IA should be considered [69]. Triazole is not recommended for empiric therapy of breakthrough infection during triazole prophylaxis and a different class of mold-active antifungal agent is required. When fever of unknown origin persists in patients without mold-active prophylaxis, empiric antifungal therapy with triazole might be considered [14, 70].

Reducing the dose or cessation of immunosuppressive agents could be a component of aspergillosis treatment. Colony-stimulating factors in neutropenic patients may also be considered. Granulocyte transfusion can be considered if the patient is unlikely to respond to standard therapy and if the anticipated duration of neutropenia is more than one week [71]. Surgery should be considered in localized disease [ex. invasive fungal sinusitis, endocarditis, osteomyelitis, focal invasion of central nervous system (CNS)]. IA is not an absolute contraindication to additional chemotherapy or stem cell transplantation. Decision must consider the risk of progressive aspergillosis during anti-neoplastic therapy versus the risk of clinical deterioration due to the aggravation of underlying hematologic diseases during delayed treatment [72, 73].

Voriconazole undergoes extensive hepatic metabolism and share metabolic pathways with many drugs. Therefore, TDM and drug interaction (ex. cyclosporin, tacrolimus, sirolimus and other CYP3A4 substrates) must be monitored for optimized therapeutic efficacy and to avoid potential toxicities. Genetic polymorphisms in CYP2C19 also contribute to serum drug levels. Common side effects include photopsia, photosensitivity, CNS disturbance, and prolonged QT interval. Amphotericin B deoxycholate, which is no longer used as primary IA treatment has many side effects including infusion-related toxicity and renal toxicity. However, some centers in Korea still use amphotericin B deoxycholate as the first line of treatment due to insurance and economic issues [73, 74].

MUCORMYCOSIS

Mucormycosis represents a group of life-threatening infections caused by fungi of the order *Mucorales*. *Mucorales*

are ubiquitous environmental fungi and cause infection in patients with diabetes mellitus, solid organ transplantation or HSCT, prolonged neutropenia, or malignancy [1]. Suspected mucormycosis requires rapid diagnostic and therapeutic intervention including medical, surgical, radiological, and laboratory team to increase survival because of its rapidly progressive and destructive nature [75]. All-cause mortality rates range from 40–80% and poorest prognosis is observed in patients with hematologic diseases and HSCT recipients [76].

Six different syndromes are grouped according to the anatomic predilection: sinusitis (rhino-orbital or rhinocerebral), pulmonary, cutaneous, gastrointestinal, disseminated, and other. Disseminated mucormycosis, usually as pulmonary mucormycosis typically develops in hematology patients with profound neutropenia [76, 77] and graft-versus-host diseases after allogeneic HSCT [78, 79]. Similar to IA, persistent fever without suspected symptoms is seen in most patients [75]. Rhino-orbito-cerebral mucormycosis typically develops in patients with diabetes mellitus, but can also be seen in patients with hematologic diseases [80].

Epidemiology

In the mid-20th century, diabetes mellitus used to be a major risk factor for mucormycosis. However, in recent years, underlying malignancy emerged as another important risk factor due to the increasing number of patients undergoing chemotherapy, immunotherapy, or HSCT [81, 82]. The most frequently reported pathogens are *Rhizopus* spp., *Mucor* spp., *Cunninghamella*, *Lichtheimia* spp. and *Rhizomucor* spp. Incidence rates vary by region or center, indicating geographical variation.

Diagnosis

The diagnosis of mucormycosis depends on the availability of imaging techniques, trained personnel, and mycological and histological investigations. In patients with hematologic diseases and suspected pulmonary mucormycosis, chest CT scan is recommended. Typical finding includes ground glass opacity surrounded by a ring of consolidation (reversed halo sign).

If mucormycosis is a potential diagnosis, biopsy is strongly recommended. It is usually suspected based on the results of direct microscopy. However, diagnosis with histomorphological basis is challenging because misidentification of *Mucorales* as *Aspergillus* species is common [83]. Culture of specimen is also strongly recommended for species identification and antifungal susceptibility testing. Frankly, identification of causative *Mucorales* does not obviously guide the choice of antifungal treatment because treatment should be started before the report. However, clinical course may be different depending on the species, leading to a better epidemiologic understanding. Immunohistochemistry with monoclonal antibodies or PCR could also be done, although still not widely available [75]. BDG is usually negative in patients with mucormycosis, as these fungi do not produce BDG [84]. However, about one-third of patients with pulmonary mucormycosis had concomitant opportunistic fungal infection according to previous study [85]. Cases of mixed fungal infection have also been reported [86]. Therefore, BDG, GM is recommended in suspected mucormycosis to support differential diagnosis or mixed IFI [75].

Treatment

Suspected and confirmed mucormycosis are medical and surgical emergencies and require rapid management. Breakthrough mucormycosis during mold-active prophylaxis is also possible [87, 88] and must be considered. Early complete surgical debridement with clean margins is strongly recommended for disease control, histopathology, and microbiologic diagnosis [89, 90]. In neutropenic patients, immediate surgery may be required; however, some still prefer surgical resection after the resolution of neutropenia and thrombocytopenia in IA [91].

For first line antifungal therapy, liposomal amphotericin B with dose of 5–10 mg/kg/day is recommended. When CNS involvement is suspected, dose of 10 mg/kg/day is needed [92]. Increased dose tends to have an increased response rate, but doses higher than 10 mg/kg/day did not result in higher blood concentrations and instead increased the creatinine level [93, 94]. Amphotericin B deoxycholate has been the drug of choice for decades but its use is limited due to toxicity. It is only recommended when there is no other option. Isavuconazole has similar efficacy with liposomal amphotericin B and could be used as first line treatment for mucormycosis [95]. Posaconazole is recommended as an alternative therapy if first line medication has side effect or is ineffective [75]. Two oral forms (tablet and syrup) are available. Posaconazole syrup is influenced by food and concomitant use of other drugs such as proton pump inhibitors. Therefore, TDM must be monitored for optimal blood trough levels [96, 97].

The duration of therapy in mucormycosis is unknown. In general, weeks to months of therapy are usually given. If the underlying immune defect (ex. neutropenia or use of immunosuppressants) is resolved, therapy can be continued until there is resolution of signs and symptoms or radiographic improvement. There is moderate support for intravenous treatment until stable disease is achieved. The decision to switch to oral monotherapy with isavuconazole or posaconazole depends on the patient's response to therapy and severity of the illness [75, 98].

ANTIFUNGAL PROPHYLAXIS AGAINST INVASIVE FUNGAL INFECTIONS

Despite improvements in diagnosis and treatment, IFI-associated mortality remains high and thus, antifungal prophylaxis represents an important strategy in patients at high risk for IFI [99].

Patients with neutropenia lasting less than 7 days are at low risk and do not require antifungal prophylaxis. Antifungal prophylaxis is strongly recommended in patients

Table 2. Antifungal prophylaxis for patients with hematologic diseases in Seoul St. Mary's Hospital (last revised January 2022).

Type of patients	Primary	Alternative
AML Induction/reinduction chemotherapy[a]	Posaconazole (T)	Posaconazole (S) Fluconazole
HMA/Venetoclas[a]		
- Secondary/refractory AML	Posaconazole (T)	Posaconazole (S)
- Relapsed AML (only in 1st and 2nd cycle)	Posaconazole (T)	Fluconazole
- Otherwise	Fluconazole	
Other chemotherapy (neutropenia >7 days)[a]	Fluconazole	
Auto-HSCT[a],[c]	Micafungin	Fluconazole Itraconazole
Allo-HSCT (pre-engraftment)[a],[c]	Micafungin	Itraconazole (S)
Allo-HSCT (in the presence of GVHD)[b]	Posaconazole (T)	Posaconazole (S) Fluconazole

[a]Start from absolute neutrophil count ≤1,000 until resolution of neutropenia. [b]Until at least 75 days from start or resolution of significant GVHD. [c]Voriconazole is only used as secondary prophylaxis in patients with previous proven or probable IPA history.
Abbreviations: AML, acute myeloid leukemia; GVHD, graft versus host disease; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplantation; S, Syrup; T, Tablet.

with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) who are in remission or undergoing induction chemotherapy as they are expected to have neutropenia for more than 7 days. Allogeneic HSCT recipients with risk factors such as GVHD are also recommended to have antifungal prophylaxis depending on the local incidence and epidemiology. Fluconazole was often used [100], but protection against non-albicans *Candida* species and mold was not warranted. Therefore, guidelines strongly suggest posaconazole as an antifungal prophylaxis for these groups [99, 101-103]. Echinocandin is susceptible in azole resistant *Candida* and *Aspergillus* and can be used as prophylaxis in both autologous and allogeneic HSCT patients [104].

Voriconazole is only used as secondary prophylaxis during HSCT in patients with a previous history of IA in Korea. Aerosolized liposomal amphotericin B inhalation was found to be effective in reducing IPA and may be considered as an option in the future, considering the increasing azole resistance [105]. New chemotherapy drugs (ex. venetoclax) with drug interaction to triazoles are continuously developed, and strategies might be delicately managed considering the risk factors [106]. An example of antifungal prophylaxis strategy in our hospital regarding guidelines mentioned above is shown in Table 2.

In addition to medical prophylaxis, environmental protection should be supervised. High risk patients should be placed in a protected environment to reduce mold exposure. High-efficiency particulate air (HEPA) filtration and maintenance of positive pressure room are examples. If protected environment is not available, a private room could be alternative. Reasonable precautions include avoidance of gardening, and not allowing plants or cut flowers to patient's room [107]. Health care workers can also play a key role in transmission [108]. Therefore, regular surveillance of IFI cases and education of workers are needed [48].

QUALITY CONTROL OF THE CLINICAL MANAGEMENT

There are guidelines recommended for the ideal managements of IFIs but following these guidelines may be challenging. To highlight the strongest recommendations and measure guideline adherence, the ECMM QUALity of Clinical management score (EQUAL score) was designed. Factors include diagnostic and follow-up procedures, and treatment parameters with different scores. Total score is measured by summing each item. Simplified figure cards for each disease showing items and weights are released for free so anyone can use. Physicians might get important recommendations concisely without reading complicated guidelines entirely. Whether a high score correlates with an outcome remains to be explored; however, these efforts might facilitate antifungal stewardship [109-111]. Previous studies reported that greater guideline adherence with a higher EQUAL *Candida* score was associated with survival among patients with candidemia [112, 113].

CONCLUSION

IFIs are related to high mortality and morbidity in patients with hematologic diseases and HSCT recipients. Diagnosis and treatment are complicated due to different epidemiology, risk factors, and immune status of the patients. There is a need to analyze the epidemiology regularly and be aware of risk factors to efficiently apply prophylactic antifungal agents. Various tests are mandatory to diagnose and treat IFIs as accurately as possible and further studies are required to improve the prognosis of IFIs in the future.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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