

# Characteristics of culture-positive invasive pulmonary aspergillosis in patients with hematologic diseases

## Comparison between *Aspergillus fumigatus* and non-*fumigatus* *Aspergillus* species

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### Abstract

While the epidemiology and clinical differences of various *Candida* spp. has been relatively well-identified, data regarding invasive aspergillosis (IA) caused by different *Aspergillus* spp. are insufficient.

We aimed to determine the epidemiology of culture-positive invasive pulmonary aspergillosis (IPA) and to compare the characteristics and outcomes of *Aspergillus fumigatus* IPA with those of non-*fumigatus* IPA in patients with hematologic diseases. All consecutive cases of IPA from 2011 to 2015 were reviewed retrospectively.

There were 430 proven/probable IPA and 76 culture-positive proven/probable IPA. Excluding cases of multiple species of fungi or cases having difficulties in species-level identification, 41 *A. fumigatus* and 22 non-*fumigatus* IPA (*Aspergillus flavus* [n=11], *Aspergillus niger* [n=6], and *Aspergillus terreus* [n=5]) were compared. There were no significant differences in baseline characteristics between the 2 groups. However, disseminated IA was more common in non-*fumigatus* IPA (2.4% vs 18.2%;  $P=.046$ ). Paranasal sinus (PNS) involvement was more common in non-*fumigatus* IPA. There was a trend towards higher peak serum galactomannan values in non-*fumigatus* IPA than in *A. fumigatus* IPA group (median 1.33 [interquartile 0.98–3.29] vs 0.97 [0.66–1.97];  $P=.084$ ). Clinical response and mortality did not differ between groups.

The culture-positive rate of proven/probable IPA was 17.7%, of which non-*fumigatus* *Aspergillus* accounted for about one-third. Disseminated IA, especially involving the PNS, was more frequent in non-*fumigatus* IPA than in *A. fumigatus* IPA.

**Abbreviations:** IA = invasive aspergillosis, IPA = invasive pulmonary aspergillosis, PNS = paranasal sinus.

**Keywords:** *Aspergillus fumigatus*, diagnosis, hematology, invasive pulmonary aspergillosis

### 1. Introduction

*Aspergillus fumigatus* is the most common pathogen causing invasive aspergillosis (IA) in patients with hematologic malignancies.

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However, several studies have reported the emergence of IA caused by non-*fumigatus* *Aspergillus* spp. such as *Aspergillus flavus* or *Aspergillus terreus*.<sup>[1,2]</sup> The clinical importance of the non-*fumigatus* *Aspergillus* spp. is based on the potential differences in in vitro susceptibilities, clinical courses, and finally the treatment outcomes of patients. In addition, there are recent reports regarding “cryptic species” among “*Aspergillus* complex” denominating a group of species that are very closely related and almost indistinguishable by morphologic methods, which might have decreased or affected susceptibility to amphotericin B deoxycholate or voriconazole.<sup>[3,4]</sup> However, species-level identification of *Aspergillus* is still limited in current routine microbiology work in many clinical settings.

While the epidemiology and clinical differences of various *Candida* spp. has been relatively well-identified during recent decades, data regarding IA caused by different *Aspergillus* spp. are insufficient. This may be attributable to the low culture-positive rate in IA, which shows only 10% to 30% of patients with IA at any time.<sup>[5,6]</sup> In addition, fungus culture may be falsely positive or negative,<sup>[5]</sup> which might be difficult to be interpreted and differentiate true infections from colonization and/or contaminations in some cases. Nevertheless, there is a need to investigate the causative fungal organisms of IA, considering the development of antimold active prophylaxis in this decade.

The aim of this study was to identify the epidemiology, characteristics, and outcomes of culture-positive proven or probable invasive pulmonary aspergillosis (IPA) cases, and to

compare the clinical characteristics of *A fumigatus* IPA and those of non-*fumigatus* IPA in patients with hematologic diseases.

## 2. Materials and methods

### 2.1. Patients and clinical setting

We retrospectively reviewed all consecutive cases of invasive fungal diseases (IFDs) from January 2011 to December 2015 at the Catholic Blood and Marrow Transplantation (BMT) Centre, Seoul St. Mary's Hospital. This is a 1300-bed, university-affiliated, tertiary hospital that performs over 500 stem cell transplantations (SCTs) annually. Serum galactomannan assay was routinely screened twice per week and examined daily for sequential 3 to 4 days if IFDs were suspected. Computed tomography (CT) was performed when (1) patients had symptoms (pleuritic chest pain, blood tinged sputum, or hemoptysis) or signs that suggest newly developed pneumonia, tenderness, or swelling around the paranasal sinus (PNS) or orbital area, ulcerating lesions or eschar in the nose; (2) neutropenic fever did not resolve within 3 to 5 days of initial empirical antibacterial agents, regardless of symptom; (3) serum galactomannan test was positive. There were no changes in the diagnostic strategies during the whole study periods.

### 2.2. Study design

Only culture-positive proven/probable IPA cases in adult ( $\geq 18$  years of age) patients with hematologic diseases were included in this study. IA of deep-seated organs without lung involvement, IPA cases involving mixed growth of 2 or more fungal organisms, or cases where the *Aspergillus* isolate could not be identified at the species level were excluded from the analysis. Respiratory specimens were considered as appropriate when they were obtained from the lower respiratory tract and demonstrated clinical significance: sputum (group 4, 5, or 6; grade of sputum quality satisfying epithelial cells  $\leq 25$ /low power field [LPF] and white blood cells [WBC]  $>25$ /LPF), bronchial washing fluid, bronchoalveolar lavage fluid, or bronchial brush according to the revised definition of IFD from the European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG).<sup>[7]</sup> Identification of mold relied mainly on the observation of morphological characteristics by clinical microbiologists in this institute during the study period. Data on baseline characteristics, results regarding IFDs (clinical, microbiologic, laboratory, and radiologic results), and outcomes of patients were collected. The Institutional Review Board of Seoul St. Mary's Hospital approved the research protocol and waived the need for informed consent due to the anonymous and retrospective design of the study (KC16RISI0623).

### 2.3. Definitions

Neutropenia was defined as an absolute neutrophil count (ANC)  $<500/\text{mm}^3$  or ANC  $<1000/\text{mm}^3$  with a predicted reduction to  $<500/\text{mm}^3$  within 2 to 3 days. Severe neutropenia was defined as an ANC  $<100/\text{mm}^3$ .<sup>[8,9]</sup> IFDs were categorized as proven or probable according to the revised definition from EORTC/MSG. Disseminated IFD was defined as involvement of  $\geq 2$  noncontiguous organs.<sup>[10,11]</sup> Responses were assessed at 6 weeks according to the previous studies with some modifications as follows.<sup>[12–14]</sup> Complete response (CR) was defined as resolution of all clinical signs and symptoms and  $>90\%$  reduction in radiologic lesions attributable to IA. Partial response (PR) was defined as clinical

improvement plus  $>50\%$  reduction in radiologic lesions attributable to IA. Stable response (SR) was defined as no or minimal improvement. Progression was defined as worsening of IA disease. In cases of IA involving  $\geq 2$  nonadjacent organs, the response was graded on the basis of the organ with the worse condition. Success was defined as CR or PR. Unsuccessful outcomes were defined as SR or failure. Mortality was assessed at 6 weeks, 12 weeks, and 1 year.

### 2.4. Statistical analysis

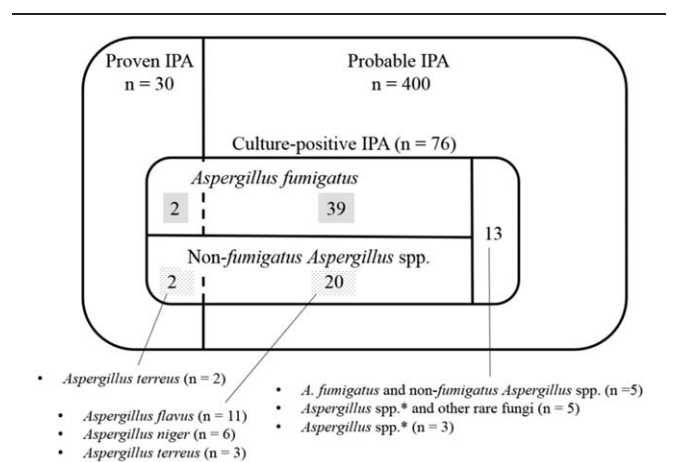
Categorical and continuous variables are presented as n (%) and median (interquartile range [IQR]). The chi-square test or Fisher exact test was used to compare categorical variables, and the Student *t* test or Mann–Whitney test was used to compare continuous variables. The Kaplan–Meier method was used to compare trends of survival. Cox proportional-hazard model was used to identify independent risk factors for 12-week mortality. A 2-tailed *P* value  $<.05$  was considered significant. Statistical analyses were performed using SPSS software version 24.0 (SPSS Korea, Seoul, Korea).

## 3. Results

### 3.1. Categories of IPA and isolated fungal organisms

During the 5 years of study period, among 521 proven/probable IFDs, 430 cases of proven/probable IPA were identified at the Catholic BMT Center. *Aspergillus* spp. were isolated from clinically significant respiratory specimens in 4 of 30 proven IPA cases and 72 of 400 probable IPA cases. The culture-positive rate of proven/probable IPA was 17.7% (76/430) (Fig. 1). Eighty-three *Aspergillus* clinical isolates were identified from 76 proven/probable IPA cases. *A fumigatus* was the most common species and accounted for 56.6% (47/83) of isolates, followed by *A flavus* (18.1%, 15/83), *Aspergillus niger* (12.0%, 10/83), *A terreus* (9.6%, 8/83), and *Aspergillus* spp. (3.6%, 3/83) without species-level identification by morphology.

To compare IPA caused by *A fumigatus* and non-*fumigatus* *Aspergillus* spp., cases with both *A fumigatus* and non-*fumigatus* *Aspergillus* spp. (n=5), IPA with combined IFD other than aspergillosis (n=5), or reported only as *Aspergillus* spp. (n=3) were excluded from the analysis. Mixed growth of non-*Aspergillus*



**Figure 1.** Categories of invasive pulmonary aspergillosis. \*Reported as *Aspergillus* spp. without species-level identification by morphology. IPA = invasive pulmonary aspergillosis.

spp. included *Penicillium scopulariopsis* (n=1), *Penicillium* spp. (n=2), *Trichosporon asahii* (n=1), and *Fusarium* spp. (n=1). After these exclusions, in all, 41 patients with proven/probable IPA caused by *A fumigatus* (*A fumigatus* group) and 22 patients with proven/probable IPA by non-*fumigatus* *Aspergillus* spp. (non-*fumigatus* group) were compared.

### 3.2. Patient characteristics

As shown in Table 1, there were no significant differences in baseline patient characteristics, including age, sex, underlying diseases, treatment for hematologic diseases, severity of neutropenia, and graft-versus-host disease (GVHD) between the *A fumigatus* and non-*fumigatus* groups. The most common underlying disease was acute myeloid leukemia (49.2%, 31/63), followed by acute lymphoblastic leukemia (19.0%, 12/63), lymphoma (11.1%, 7/63), multiple myeloma (11.1%, 7/63), myelodysplastic syndrome (3.2%, 2/63), aplastic anemia (3.2%, 2/63), and chronic lymphocytic leukemia (1.6%, 1/63). SCT was the most common treatment (54.0%, 34/63) for underlying hematologic diseases before the diagnosis of IPA, followed by intensive chemotherapy (22.2%, 14/63). Of the SCT recipients, 73.5% (25/34) of patients received immunosuppressive therapy for acute (grade ≥II) or chronic GVHD as the main treatment at the time of IPA diagnosis.

### 3.3. Comparison of *A fumigatus* IPA and non-*fumigatus* *Aspergillus* IPA

The clinical course and outcomes of patients are shown in Table 2. Serum galactomannan positivity was confirmed in about half of the cases, which did not differ between the *A fumigatus* and non-*fumigatus* groups. However, there was a trend towards higher peak serum galactomannan levels in the non-*fumigatus* group (median 1.33, IQR 0.98–3.29) compared with the *A fumigatus* group (median 0.97, IQR 0.66–1.97) ( $P=.084$ ).

As shown in Table 2, dissemination rate was significantly higher in the non-*fumigatus* group (18.2% [4/22]) than *A fumigatus* group (2.4% [1/41]) ( $P=.046$ ). Among the non-*fumigatus* *Aspergillus* species, *A terreus* showed significantly

**Table 1**  
Patient characteristics.

Characteristics, n (%)	<i>Aspergillus fumigatus</i> (n=41)	Non- <i>fumigatus</i> <i>Aspergillus</i> spp. (n=22)	P
Age	52.7 ± 13.3	52.3 ± 16.8	.906
Male	24 (58.5)	13 (59.1)	.966
Underlying diseases			
Myeloid malignancies	23 (56.1)	10 (45.5)	.261
Lymphoid malignancies	15 (36.6)	12 (54.5)	
Others	3 (7.3)*	0 (0)	
Treatment			
Cytotoxic chemotherapy	10 (24.4)	4 (18.2)	.533
Stem cell transplantation	23 (56.1)	11 (50.0)	
Others†	8 (19.5)	7 (31.8)	
Neutropenia (ANC <500/mm <sup>3</sup> )	8 (19.5)	6 (27.3)	.480
Severe neutropenia (ANC <100/mm <sup>3</sup> )	8 (19.5)	4 (18.2)	.898
GVHD	17 (41.5)	8 (36.4)	.693

ANC=absolute neutrophil count; GVHD=graft-versus-host disease.

\*Aplastic anemia (n=2), hemophagocytic lymphohistiocytosis (n=1).

†Noncytotoxic chemotherapy (n=4), immunosuppressive therapy (n=2), supportive care only (n=9).

**Table 2**  
Clinical course and outcomes of patients.

Characteristics, n (%)	<i>Aspergillus fumigatus</i> (n=41)	Non- <i>fumigatus</i> <i>Aspergillus</i> spp. (n=22)	P
IPA category			
Proven	2 (4.9)	2 (9.1)	.606
Probable	39 (95.1)	20 (90.9)	
Serum GM ≥ 0.5	20 (48.8)	10 (45.5)	.801
First positive serum GM level, median (IQR)	0.72 (0.58–1.08)	0.96 (0.58–1.55)	.283
Peak serum GM level	0.97 (0.66–1.97)	1.33 (0.98–3.29)	.084
Disseminated aspergillosis	1 (2.4)*	4 (18.2)†	.046
PNS involvement	0 (0)	2 (9.1)	.050
Day 42 response assessment			
CR	2 (4.9)	2 (9.1)	.914
PR	16 (39.0)	9 (40.9)	
SR	12 (29.3)	6 (27.3)	
Progression	11 (26.8)	5 (22.7)	
Day 42 all-cause mortality	11 (26.8)	6 (27.3)	.970
Day 84 all-cause mortality	17 (41.5)	9 (40.9)	.966
Day 360 all-cause mortality	24 (63.2)	13 (61.9)	.924
Recurrence of IPA	5 (13.2)	3 (15.0)	.569

CR=complete response, GM=galactomannan, IPA=invasive pulmonary aspergillosis, IQR=interquartile range, PNS=paranasal sinus, PR=partial response, SR=stable response.

\*Kidney (n=1).

†PNS (n=2), bone (n=1), external auditory canal (n=1).

higher dissemination rate (40% [2/5]) when compared with other non-*terreus* *Aspergillus* species (5.2% [3/58]) ( $P=.046$ ). Five disseminated aspergillosis cases developed in patients who had risk factors of disseminated fungal infection, such as neutropenia, chronic GVHD, and steroid use, whereas underlying diseases were varied. Organs to which dissemination was observed included PNS (n=2), bone (n=1), kidney (n=1), and external auditory canal (n=1).

The initial choice of antifungal agent for the treatment of IPA was amphotericin B deoxycholate or liposomal amphotericin B (52.4%) and voriconazole (44.4%), followed by voriconazole maintenance therapy. The distribution of antifungal agent usage showed no difference between groups ( $P=.829$ ). Treatment success at 6 weeks (43.9% vs 50.0%;  $P=.914$ ), recurrence of IPA (13.2% vs 15.0%;  $P=.569$ ), and all-cause mortality at 6 weeks (26.8% vs 27.3%;  $P=.970$ ), 12 weeks (41.5% vs 40.9%;  $P=.966$ ), and 1 year (63.2% vs 61.9%;  $P=.924$ ) were not statistically different between groups (Table 2).

## 4. Discussion

We reported herein the culture-positive proven/probable IPA cases in patients with hematologic diseases. In addition, as there are relatively few data regarding *Aspergillus* spp. from IPA patients due to the lower culture-positive rate, we compared the characteristics and outcome between IPA caused by *A fumigatus* and non-*fumigatus* *Aspergillus* spp. During the study period, the culture-positive rate of proven/probable IPA was 17.7% at this institute. Interestingly, however, we found that the culture-positive rate has doubled to 38% since January 2016, accompanied by clinicians' active diagnostic efforts—increase of fungus culture prescriptions and performance rates—to identify causative *Aspergillus* spp. from patients with suspected IPA. About 50% of our culture-positive cases showed negative results on the serum galactomannan assay, despite compatible

clinical manifestations of IPA. In such cases, the diagnostic evidence was strengthened from possible to probable categories based on the fungus culture of appropriate respiratory specimens according to the EORTC/MSG criteria.

In this study, *A. fumigatus* was the dominant species (65%), whereas in a previous report non-*fumigatus* spp. comprised 70% of IA cases.<sup>[15]</sup> This supports the idea that distribution of *Aspergillus* spp. causing IA can show institution-specific differences. Furthermore, the increase of non-*fumigatus Aspergillus* spp. can be related to the previous exposure to azole or amphotericin B due to the antifungal selection pressure, and azole resistance can also be detected in non-*fumigatus Aspergillus* in such cases.<sup>[16]</sup> Antimold active prophylaxis became available to significant number of GVHD patients since July 2015 based on reimbursement practices in Korea, which could affect the future mold epidemiology.

Non-*fumigatus Aspergillus* spp., which comprised one-third of culture-positive IPA, presented with multiple organ involvement more frequently, especially PNS, compared with *A. fumigatus* IPA. Although there was a relatively small number of disseminated cases in culture-positive IPA patients, this finding suggests that upon identification of non-*fumigatus Aspergillus* spp., there is a need to identify the foci of IA other than the lung. The characteristics and differences in the pathogenicity of each *Aspergillus* spp. depends on the various factors such as conidial size, virulence, germination rate, adhesion, or phagocytosis. For example, *A. flavus*, the second most common pathogenic species of IA, produces conidia larger than *A. fumigatus*. Such characteristics of *A. flavus* is related to the sinus aspergillosis, whereas *A. fumigatus* is known as the main cause of IPA since *A. fumigatus* conidia can reach pulmonary alveoli easier.<sup>[17]</sup> On the contrary, *A. terreus* is known to have better sporulation capacity in tissue and blood, which can lead to a higher rate of dissemination compared with *A. fumigatus*.<sup>[18,19]</sup> In the present study, the dissemination rate was 40% in *A. terreus* IPA and 2.4% in *A. fumigatus* IPA, which is consistent with an Austrian study where proven IA caused by *A. terreus* is common in leukemia patients with 60% of dissemination rate.<sup>[19]</sup> However, there are intraspecies variations in virulence or pathogenicity of *Aspergillus* spp., and human data are still insufficient. In addition, host factor of patients can also significantly affect the dissemination rate and clinical course. Therefore, long-term human clinical data accumulation is necessary to elucidate the relationship between IA and different *Aspergillus* spp.

Currently, the diagnosis of IPA primarily depends on indirect biomarkers such as serum galactomannan or 1, 3,  $\beta$ -D-glucan assays.<sup>[20]</sup> While specific antibodies and molecular methods have been developed, there still remain unmet needs for diagnosis of aspergillosis.<sup>[21]</sup> Since culture result from an appropriate specimen is the gold standard for diagnosis of infection, efforts to identify causative *Aspergillus* spp. should be emphasized to improve the outcome based on a detailed pathogen diagnosis. Sputum culture with an adequate collection procedure could be helpful when performed in a timely manner for diagnosis and managing IPA. The strength of this study is that it was based on the infectious diseases specialist's clinical judgment of sputum culture results.

The limitation of this study is that it is based on data collected before establishing an in vitro susceptibility test with cryptic species-level identification of *Aspergillus* from clinically significant fungal pathogen of IFD patients. At our institute, identification of fungal pathogens is now performed by using both morphological characteristics and sequence-based

molecular methods. Further investigations by our study group are ongoing. Differences between non-*fumigatus Aspergillus* and *A. fumigatus* IPA, and furthermore, the characteristics of each species, should be studied by means of an in vitro susceptibility test of *Aspergillus* isolates from a large number of patients.

## 5. Conclusions

In conclusion, non-*fumigatus* comprises one-third of culture-positive IPA cases in this institute. Multiple organ involvement should be checked in non-*fumigatus* IPA compared with *A. fumigatus* IPA.

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