



Original Article

# Breakthrough invasive fungal diseases during voriconazole treatment for aspergillosis: A 5-year retrospective cohort study

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## Abstract

Breakthrough invasive fungal diseases (bIFDs) during voriconazole treatment are concerning, as they are associated with high rates of mortality and pathogen distribution. To evaluate the prevalence, incidence, patient characteristics, including IFD events, and overall mortality of bIFDs during voriconazole treatment for invasive aspergillosis (IA). We retrospectively analyzed the medical records of consecutive patients who had undergone voriconazole treatment for IA and who had bIFD events between January 2011 and December 2015. Eleven bIFD events occurred in 9 patients. The prevalence and incidence of bIFDs were 2.25% (9/368) and 0.22 cases per year, respectively. Overall mortality was 44.4% (4/9). The severity of the illness and persistence of immunodeficiency, mixed infection, and low concentration of the treatment drug at the site of infection were identified as possible causes of bIFDs. Seven of 11 events (63.6%) required continued voriconazole treatment with drug level monitoring. In 4 (36.3%) cases, the treatment was changed to liposomal amphotericin B. Two cases resulted in surgical resection (18.2%). Clinicians should be aware that bIFDs during voriconazole treatment for IA can occur, and active therapeutic approaches are required in these cases.

**Key words:** Mycoses, Voriconazole, Aspergillosis, Breakthrough invasive fungal disease.

## Introduction

Voriconazole is a broad-spectrum antifungal agent that is effective against most *Aspergillus* species. It is now the ini-

tial standard treatment of choice for invasive aspergillosis (IA) in immunocompromised patients.<sup>1</sup> A previous report suggested that voriconazole improves clinical responses and survival rates compared to initial treatment with

amphotericin B deoxycholate.<sup>1</sup> Invasive fungal diseases (IFDs) that occur during the ongoing use of systemic antifungal agents indicate an important, unresolved problem in the clinical management of immunocompromised patients.<sup>2</sup> Breakthrough infections have been defined as the occurrence of IFDs while the patient is receiving antifungal agents, including agents administered for both prophylaxis and therapy.<sup>3</sup> Some studies have reported breakthrough mucormycosis during voriconazole treatment, which is commonly used for mold prophylaxis or as a treatment for invasive IA.<sup>4–8</sup> Kontoyiannis et al.<sup>8</sup> suggested that previous prophylactic treatment with voriconazole was an independent risk factor for the development of mucormycosis, rather than IA, in patients with hematological malignancies. Another report demonstrated a high overall mortality rate (73%) associated with breakthrough mucormycosis during voriconazole treatment.<sup>6</sup>

As aforementioned, breakthrough IFDs (bIFDs) such as mucormycosis, candidiasis, and other rare fungal infections during voriconazole treatment are concerning, as they are associated with high rates of mortality and may affect pathogen distribution. There is currently a paucity of clinical study data regarding this topic, and prospective controlled clinical studies have not been feasible.<sup>2</sup>

Accordingly, the aims of the current study were to evaluate the prevalence, incidence, patient characteristics, and prognosis of bIFDs during voriconazole treatment for IA, and to assess the distributions of pathogens during each bIFD episode. Furthermore, we suggest some therapeutic approaches for the treatment of bIFDs during voriconazole treatment for IA based on our experience with a large cohort from a single center.

## Subjects and methods

A cohort of patients aged over 18 years and diagnosed with IA between January 2011 and December 2015 were assessed. We retrospectively analyzed the medical records of consecutive patients who had received voriconazole treatment for IA at Seoul St. Mary's Hospital, The Catholic University, Korea, during in this period. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, The Catholic University, Korea with a waiver for informed consent (KC16RISI0102).

## Definitions

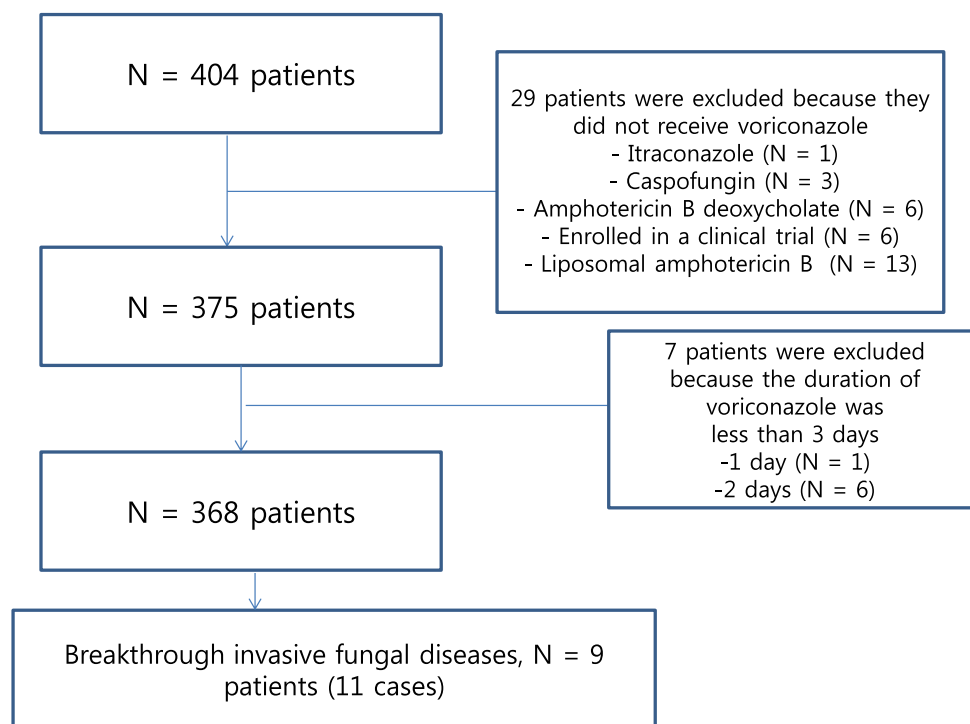
Classification of IA was based on the European Organization for the Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria, which requires positive diagnosis by host, radiologic and microbiologic as-

sessments.<sup>9</sup> A positive diagnosis of IA by microbiological assessment required a positive culture of *Aspergillus* sp. from clinically significant specimens<sup>10</sup> and/or the detection of a galactomannan assay index cut-off of  $\geq 0.5$  during at least one time point using patient serum. Only probable or proven IFDs according to the revised EORTC/MSG criteria were included in the analysis.<sup>9</sup>

An IFD was considered to be a bIFD if the (1) causative organism was different from that originally detected before the commencement of voriconazole therapy, (2) occurrence was detected  $\geq 3$  days after the initiation of voriconazole therapy, or (3) subsequent infection occurred within 14 days after the discontinuation of voriconazole therapy.<sup>4,11</sup> The day of diagnosis was defined as the day on which the first diagnostic procedure identifying the IFD was performed. If two species were cultured at the time of the secondary event but not concurrently, they were defined as two independent infections. A mixed infection was defined as an infection with two or more organisms detected concurrently at the time of the breakthrough event. Cases of worsening IA, which included immune reconstitution inflammatory syndrome (IRIS)<sup>12</sup> or idiopathic pneumonitis syndrome,<sup>13</sup> were excluded by two independent infectious disease specialists. Neutropenia was defined as an absolute neutrophil count  $< 500$  cells/mm<sup>3</sup> or an absolute neutrophil count that was expected to be  $< 500$  cells/mm<sup>3</sup> within 2–3 days.<sup>14</sup> Other definitions for neutropenic fever according to Lee et al. were followed.<sup>14</sup> Neutropenia duration was defined as the time from initial aspergillosis treatment to the time of bIFD. Overall mortality was defined according to survival within the 3-month follow-up period from when the bIFD was diagnosed.

## Voriconazole therapeutic drug monitoring

Serum voriconazole trough levels were measured using high performance liquid chromatography (HPLC) coupled with tandem mass spectrometry (LC-MS/MS), as described previously with minor modifications.<sup>15</sup> Following protein precipitation (10  $\mu$ l of serum plus 40  $\mu$ l of a zinc sulfate [100 mmol/l] solution, plus 100  $\mu$ l of acetonitrile, which contained the internal standard, ketoconazole at 1 mg/l), 3  $\mu$ l of the supernatant was injected into the LC-MS/MS system, which consisted of an Alliance 2795 HT HPLC device (Waters Corp., Milford, MA, USA) and a Quattro Premier XE tandem mass spectrometer (Waters Corp., Milford, MA, USA). Separation was achieved using a Security-Guard C<sub>18</sub> cartridge column (4.0  $\times$  2.0 mm; Phenomenex, Macclesfield, UK). For HPLC, voriconazole was eluted by isocratic flow with 0.1% (v/v) formic acid, dissolved in 75% methanol containing 2 mM of ammonium acetate. The



**Figure 1.** Screening of patients with breakthrough invasive fungal diseases during voriconazole treatment.

column flow rate was 0.25 ml/min, and the column temperature was maintained at 55 °C. The electrospray ionization source was operated in positive mode with a capillary voltage of 1 kV and a cone voltage of 40 V. Compounds were detected using the multiple reaction monitoring mode using ion transitions of  $m/z$  350.0  $\rightarrow$  224.1 for voriconazole and  $m/z$  531.1  $\rightarrow$  489.1 for ketoconazole. A 3-point set of lyophilized calibrators, and three concentrations of lyophilized quality control materials from Chromsystems were used, and the linearity of the standard curve ranged 0.1–10 mg/l. Blood sampling was performed at least 4 days after starting therapy, immediately before the subsequent voriconazole dose. The appropriate target range for the voriconazole trough levels was 1–5.5 mg/l.<sup>16–18</sup>

### CYP2C19 genotyping

DNA extracted from buccal swabs was used for CYP2C19 genotyping. CYP2C19 genetic polymorphisms were determined using a Seeplex<sup>®</sup> CYP2C19 ACE Genotyping system (Seegene, Seoul, Korea) according to the manufacturer's instructions. Briefly, a multiplex polymerase chain reaction system was used to detect *CYP2C19\*2* and *CYP2C19\*3* alleles. The *CYP2C19\*17* allele was identified using polymerase chain reaction-restriction fragment length polymorphism analysis and sequencing as described previously.<sup>19</sup> CYP2C19 phenotypic subgroups were classified as follows: homozygous extensive metabolizers (EMs), carriers of 2

wild-type alleles (*CYP2C19\*1*) or 1 wild-type allele and 1 *CYP2C19\*17* allele; heterozygous extensive metabolizers (HEMs), carriers of 1 null allele and 1 wild-type allele; and poor metabolizers (PMs), carriers of 2 null alleles (most commonly *CYP2C19\*2* or *CYP2C19\*3*).<sup>20,21</sup>

### Fungus identification

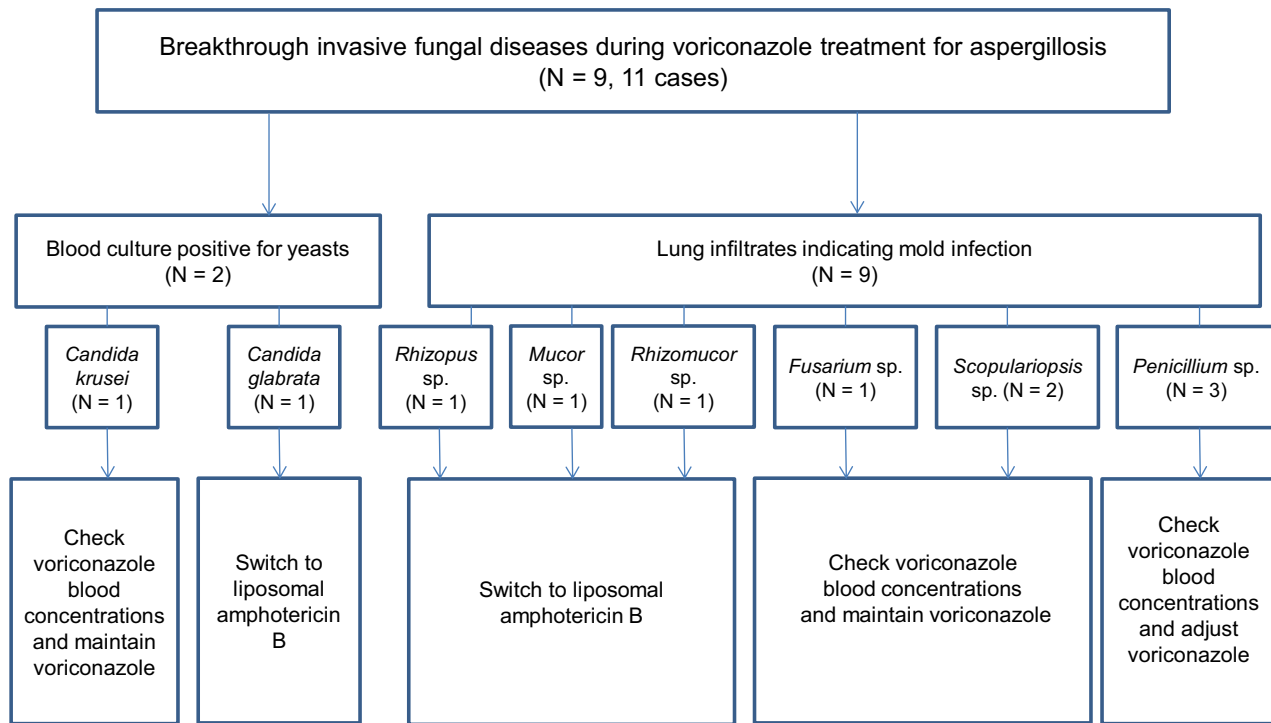
Identification of fungus was performed by automated chemical tests with API 20C; bioMérieux, Marcy l'Etoile, France) (Vitek 2 system; Vitek 2 YST; bioMérieux), followed by visual inspection.<sup>22</sup>

## Results

### Patients' characteristics

Four hundred and four patients underwent antifungal treatment for probable or proven IA between January 2011 and December 2015. Among them, 51 patients had proven IA, and the remainder (353 patients) had probable IA. Thirty-six patients were excluded, because voriconazole treatment was not provided ( $n = 29$ ) (Fig. 1) or the duration of voriconazole treatment was less than 3 days ( $n = 7$ ) (Fig. 1).

Nine patients had bIFD. Among them, considering the independent cases, total 11 cases of bIFD events occurred as shown in Fig. 2. The prevalence and incidence of bIFDs



**Figure 2.** Diagram of pathogens and treatment for breakthrough invasive fungal diseases.

during the study period were 2.25% (9/368 patients) and 0.22 cases per year, respectively. The clinical and demographic characteristics of patients with bIFDs who received voriconazole for IA are shown in Table 1. The median patient age was 56 years (range 32–74 years), and 77.8% were male. Underlying hematologic diseases affecting these patients included acute myeloid leukemia (6/9 patients, 66.7%) and acute lymphoblastic leukemia (3/9, 33.3%). More than half of the affected patients (5/9, 55.6%) had undergone stem cell transplantation (SCT). Two patients (22.2%) had undergone matched sibling donor bone marrow transplantation (BMT), and this was followed by matched unrelated donor BMT (1/9, 11.1%), matched unrelated donor peripheral blood SCT (1/9, 11.1%) and/or double cord blood transplantation (1/9, 11.1%). Both of these patients received chemotherapy (2/9, 22.2%) and conservative care (2/9, 22.2%). Among the patients with SCT, 80% (4/5) experienced acute or chronic graft-versus-host-disease (GVHD). Of the total IFD patients, 77.8% (7/9) were diagnosed with neutropenia. The median duration of neutropenia was 21.5 days (range 14–52 days) continuously without an event of neutropenic recovery. Of the total IFD patients, 77.8% (7/9) received prednisolone ( $\geq 1$  mg/kg/day). Voriconazole treatment was indicated due to proven and probable IA in 22.2% (2/9) and 77.8% (7/9) of patients, respectively. The median duration of breakthrough infection after commencement of voriconazole was 33 days (range 3–98 days).

CYP2C19 genotyping revealed that 88.9% (8/9) of the total IFD patients had the heterozygous extensive metabolizer genotype. Therapeutic drug monitoring (TDM) analysis showed that almost all of the patients (7/9, 77.8%) received approximately 1–5 mg/L of voriconazole. The sites of bIFDs were the lung (7/9, 77.8%) and bloodstream (2/9, 22.2%).

#### Possible causes of bIFD during voriconazole treatment

Reference to a previous report and analysis of individual cases<sup>23</sup> enabled the determination of possible causes of bIFDs during voriconazole treatment. These were identified as host factor, mixed infection, and low concentration of the drug at the site of infection (Table 2). The host factor was divided into two categories: the severity of the illness and immunodeficiency. The severity of the illness was determined by SCT, which had been performed in 63.6% (7/9) of patients. Immunodeficiency was identified by prolonged neutropenia in 54.5% (6/11) of cases, GVHD in 36.4% (4/11) of cases, and corticosteroid use in 81.8% (9/11) of cases. Of the total IFD cases, 9.1% (1/11) involved mixed infection at the time of diagnosis with species such as *Aspergillus* sp. and *Rhizomucor* sp. Concerning the low concentration of the drug at the site of infection, 9.1% of the total cases (1/11) had a low TDM level (trough level  $< 1$  mg/l). Moreover, 9.1% of cases (1/11) were determined

**Table 1.** Clinical and demographic characteristics of patients with breakthrough invasive fungal diseases who receiving voriconazole for invasive aspergillosis.

Characteristics	Breakthrough IFD (N = 9)
Age, median (range) years	56 (32–74)
Male, no (%)	7 (77.8%)
Underlying disease, no (%)	
AML	6 (66.7%)
ALL	3 (33.3%)
Treatment	
CTx.	2 (22.2%)
SCT	5 (55.6%)
Conservative care	2 (22.2%)
GVHD, no (%)	4 (4/5, 80%)
Neutropenia < 500/mm <sup>3</sup> , yes	7 (77.8%)
Duration of neutropenia, median (range) days	21.5 (14–52)
Corticosteroids; prednisolone ≥1 mg/kg/day, no (%)	7 (77.8%)
Indication for voriconazole, no (%)	
Proven category	2 (22.2%)
Probable category	7 (77.8%)
Day of breakthrough infection after start of voriconazole, median (range) days	33 (3–98)
CYP2C19 genotype	
Homozygous EM, no (%)	0 (0%)
Heterozygous EM, no (%)	8 (88.9%)
PM, no (%)	0 (0%)
Not done, no (%)	1 (11.1%)
Voriconazole TDM (mg/l)	
<1	1 (11.1%)
1–5	7 (77.8%)
>5	1 (11.1%)
Site of breakthrough IFD	
Lung	7 (77.8%)
Bloodstream	2 (22.2%)

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CTx, chemotherapy; SCT, stem cell transplantation; GVHD, graft versus host disease; IA, invasive aspergillosis; EM, extensive metabolizer; PM, poor metabolizer; TDM, therapeutic drug monitoring; IFD, invasive fungal disease.

to involve a poor vascular supply. For example, patient 9 had an abscess and necrotic tissue, which originated from a liver abscess.

### Management and outcome

The management of all bIFD cases at our center is shown in Table 3. Seven of 11 cases (63.6%) required continued voriconazole treatment, and weekly TDM of voriconazole levels. Four cases (36.3%) required a change of medication to liposomal amphotericin B (3–5 mg/kg/day). Moreover, 2 of 11 cases (18.2%) underwent surgical resection, including lobectomy of the lung.

**Table 2.** Possible causes of breakthrough Invasive fungal diseases during voriconazole treatment.

Causes of antifungal therapy failure	N = 11 (%)
Host factor	
Severity of illness	
SCT, yes	7 (63.6%)
Persistence of immunodeficiency (e.g. neutropenia or use of corticosteroids)	
Prolonged neutropenia	6 (54.5%)
GVHD	4 (36.4%)
Receipt of corticosteroids (prednisolone ≥1 mg/kg/day)	9 (81.8%)
Mixed infection with other invasive fungal infection	1 (9.1%)
Low concentration of the drug at the site of infection	
Pharmacokinetic and pharmacodynamic (trough level <1 mg/l)	1 (9.1%)
Poor vascular supply (e.g., abscess and necrotic tissue)	1 (9.1%)

Abbreviations: SCT, stem cell transplantation; GVHD, graft versus host disease.

**Table 3.** Management of breakthrough invasive fungal diseases.

Management	Total (N = 11) (%)
<b>Medical management</b>	
Voriconazole maintenance with TDM, no (%)	7 (63.6%)
Change to liposomal amphotericin B, no (%)	4 (36.3%)
<b>Surgical management</b>	
Surgery (Lobectomy), no (%)	2 (18.2%)

Abbreviation: TDM, Therapeutic drug monitoring.

Detailed patient characteristics, including preexisting medical conditions, and progress after bIFD diagnosis, are shown in Table 4. The bIFD events per patient are described using patient numbers (i.e., 1, 2, 3, 4-1, 4-2, 5-1, 5-2, 6, 7, 8, and 9); numbers 4-1 and 4-2 represent two episodes of bIFD in the same patient. The primary site of IA was the lung (10/11 cases, 90.9%). There was a single case of infection primarily affecting the liver (1/11 cases, 9.1%). The causative bIFD pathogens varied and included *Rhizopus* sp., *Fusarium* sp., *Penicillium* sp., *Scopulariopsis* sp., *Candida krusei*, *Rhizomucor* sp., *Candida glabrata*, and *Mucor* sp. The treatment duration after bIFDs was 44 days (range 6–108 days). The overall mortality rate of patients within the 3 months following bIFDs was 44.4% (4/9). During the period of bIFDs, there were three incidences of bacterial coinfection with *Enterococcus faecalis*, *Stenotrophomonas maltophilia*, and *Escherichia coli*.

Table 4. Outcome of breakthrough invasive fungal diseases.

Pt.-case	Gender/Age	Medical condition before breakthrough IFD		Characteristics and progress of breakthrough IFD						
		Underlying disease and Tx.	Indication for VOR (organ)	Duration of VOR Tx. before breakthrough IFD (days)	Site of breakthrough IFD	Fungal Organism	Management	Tx. duration after breakthrough IFD (days)	Co-existing bacteremia	Outcome
1	M/52	AML s/p MUD BMT	Probable (Lung)	13	Lung	<i>Rhizopus</i> sp.	Change to L-AMB	6		Death
2	M/70	AML, conservative care	Probable (Lung)	4	Lung	<i>Fusarium</i> sp.	Maintain VOR w/ TDM	52		Survival
3	M/43	ALL s/p MSD BMT	Proven (Lung)	44	Lung	<i>Penicillium</i> sp.	Maintain VOR w/ TDM	65		Survival
4-1	M/47	ALL s/p MUD PBSCT	Probable (Lung)	22	Lung	<i>Scopulariopsis brevicaulis</i>	Maintain VOR w/ TDM	108		Survival
4-2	-	-	-	98	Lung	<i>Penicillium</i> sp.	Maintain VOR w/ TDM	68		-
5-1	F/32	ALL s/p MSD BMT	Probable (Lung)	16	Lung	<i>Scopulariopsis</i> sp.	Maintain VOR w/ TDM	69		Death
5-2	-	-	-	53	Lung	<i>Penicillium</i> sp.	Maintain VOR w/ TDM	7		-
6	M/74	AML, conservative care	Probable (Lung)	3	Bloodstream	<i>Candida krusei</i>	Maintain VOR w/ TDM	9	<i>Enterococcus faecalis</i>	Death
7	M/37	AML s/p DCBT	Probable (Lung)	92	Lung	<i>Rhizomucor</i> sp. & As- <i>pergillus</i> sp.	Change to L-AMB & lobectomy	36		Survival
8	M/56	AML s/p Consolidation CTx	Probable (Lung)	33	Bloodstream	<i>Candida glabrata</i>	Change to L-AMB	21	<i>Stenotrophomas maltophilia</i> & <i>Escherichia coli</i>	Death
9	F/63	AML s/p Consolidation CTx	Proven (Liver)	90	Lung	<i>Mucor</i> sp.	Change to L-AMB & lobectomy	44		Survival

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblast leukemia; MUD, matched unrelated donor; MSD, matched sibling donor; BMT, bone marrow transplantation; PBSCT, peripheral blood stem transplantation; DCBT, double cord blood transplantation; sp, species; Pt, patient; CTx., chemotherapy; Tx., treatment; w/, with; TDM, therapeutic drug monitoring; VOR, voriconazole; L-AMB, liposomal amphotericin B.

## Discussion

Breakthrough IFDs (bIFD) have previously been reported among immunocompromised patients who have received systemic antifungal agents, including azole drugs such as fluconazole, itraconazole, or echinocandin.<sup>2,6,24–28</sup> However, current data concerning the prevalence, incidence, and patient characteristics of bIFD, especially due to IA, in those receiving voriconazole, are limited.

The present study describes the characteristics of patients and clinical management of bIFD episodes at a single medical center over a period of 5 years. There were several interesting findings in our retrospective study that will aid the implementation of improved treatment protocols for overall IFD in the future. The analysis demonstrated a bIFD prevalence of 2.25% and an incidence of 0.22 cases per year. The overall mortality after bIFDs was 44.4%. The overall mortality in our study was lower than that reported in a previous study assessing breakthrough mucormycosis during voriconazole treatment (73%).<sup>6</sup>

When *Fusarium* sp. or *Penicillium* sp. were grown as bIFD pathogens, TDM of voriconazole was useful for determining whether further treatment was needed. However, it was difficult to determine the optimal treatment in some cases. Two similar episodes occurred in patients 4 and 5, whereby the initial cultures grew *Scopulariopsis* sp. and the follow-up cultures grew *Penicillium* sp. Infection caused by *Penicillium* sp. is most commonly due to *P. marneffei*. In our study, *Penicillium* sp. was cultured from bronchoalveolar lavage and adequate sputum specimens during several independent assessments, and considering the patient's rapidly declining clinical situation, we regarded *Penicillium* sp. as a pathogen.<sup>29</sup> Interestingly, patient 4 survived, but patient 5 died of post-operative bleeding after a heart-lung transplantation due to bronchiolitis obliterans, and this was independent of the bIFD. There were also two interesting cases where *Candida* sp. growth was observed (patients 6 and 8). *C. krusei* was cultured from a blood sample obtained from patient 6, and voriconazole was maintained using TDM. Subsequently, the patient died. However, he had coexisting *E. faecalis* bacteremia, and thus the cause of death was unclear. Based on this case, when a blood culture results in *C. glabrata* growth as bIFD, voriconazole should be changed to liposomal amphotericin B immediately. Patient 8 also died and had coexisting *S. maltophilia* bacteremia. Catheters were not removed in either of these cases. However, it was thought that catheter-related bacteremia was an unlikely cause, as the differential time to positivity was negative. Considering these candidemia episodes retrospectively, removal of the catheters may have been beneficial, regardless of the differential time to positivity. A respiratory specimen from patient 1 yielded

*Rhizopus* sp. Although voriconazole was changed to liposomal amphotericin B treatment, his clinical status rapidly deteriorated, and he died within 3 days after starting treatment with liposomal amphotericin B. In contrast, *Rhizomucor* sp. was cultured from the respiratory tract of patient 7 after an onset period of over 90 days. Despite voriconazole being replaced with liposomal amphotericin B for the adequate treatment of bIFD, and treatment being administered for over 2 weeks, his lesion did not improve. Therefore, surgery, including lobectomy of the lung, was performed. Subsequently, he survived and received further liposomal amphotericin B treatment for more than 3 weeks. Specimen pathology confirmed IA. In this case, the aspergillosis persisted, and newly developed *Rhizomucor* sp. infection occurred. It was therefore thought that these fungi were concurrently infecting the patient. Patient 9's case was also of interest. Although she had IA affecting the liver and was treated with voriconazole for over 10 weeks, bIFD occurred in her lung after a prolonged period. Considering this rare pathogen, surgery, including lobectomy of the lung, was performed. Specimen pathology confirmed mucormycosis, and therefore, liposomal amphotericin B treatment was initiated. After 44 days, liposomal amphotericin B was discontinued. The patient required ongoing voriconazole treatment for hepatic IA, as at the time of the last consultation, her immunodeficiency and liver aspergillosis had persisted.

There were a number of limitations in this study. First, it was a small retrospective study performed only at a single center. Second, precise identification of the fungal pathogens using sequencing methods was not possible, and antifungal agent sensitivity tests were not performed. Third, the duration of some breakthrough events were short. In these cases, it was not possible to determine whether the newly detected fungal species had grown concurrently with *Aspergillus* sp., or whether *Aspergillus* sp. alone was present before confirmation by autopsy. *Fusarium* sp. breakthrough events were more difficult to confirm during this short time, as cross-reactivity with *Aspergillus* sp. can occur using galactomannan assays. Therefore, a consensus on the definition of bIFD like that for IFD established by the EORTC/MSG IFD is required.<sup>30</sup>

Nevertheless, this study has some important educational results. First, the persistence of poor patient immunity or immunodeficiency, despite prolonged treatment with voriconazole for IA using TDM, may be indicative of breakthrough IA. Immunodeficiency can commonly be identified by prolonged neutropenia, GVHD, or strong immunosuppression. Clinicians should be mindful of bIFD, instead of simply diagnosing the patient with IRIS or worsening IA. Second, our experiences support the use of TDM to adjust voriconazole doses, or alter treatment to a broad-spectrum agent such as liposomal amphotericin B when required.

Third, further confirmation of the diagnosis may be required, in combination with consideration for surgery, such as lobectomy of the lung. The current Infectious Diseases Society of America guidelines recommend surgery for histological diagnoses, the removal of residual infiltrates prior to subsequent chemotherapy cycles, acute hemoptysis, the prevention of bleeding where fungal lesions have vessel involvement, and the reduction of fungal burden.<sup>31</sup> We suggest adding an indication for surgery: symptoms suggestive of bIFDs.

Clinicians should be aware that bIFDs can occur during appropriate voriconazole treatment using TDM. Clinicians may need to employ active therapeutic approaches without hesitation to resolve bIFDs.

### Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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