



# Breakthrough Invasive Fungal Infections in Patients with Acute Myeloid Leukemia

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## Abstract

**Objectives** We sought to determine the occurrence, risk factors, effect of antifungal prophylaxis, and outcomes of invasive fungal infections (IFIs) in patients with acute myeloid leukemia (AML).

**Patients and Methods** We performed a retrospective analysis of all adult patients admitted to the University of Michigan Health System for AML over a 3-year period from 2010 to 2013. We determined comorbidities, hematopoietic cell transplant (HCT) status, antifungal prophylaxis, proven and probable IFI, and outcomes at 12 weeks after initiation of appropriate antifungal therapy.

**Results** Of 333 patients in our cohort, 116 of whom had received a HCT, 98 (29%) developed an IFI. Of the 30 (9%) patients who had a proven or probable IFI, 18 had breakthrough infection while on micafungin

( $n = 5$ ), voriconazole ( $n = 4$ ), posaconazole ( $n = 5$ ), or fluconazole ( $n = 4$ ). Breakthrough IFIs were due to *Aspergillus* species ( $n = 11$ ), other molds ( $n = 4$ ), and *Candida* species ( $n = 3$ ). Factors associated with breakthrough IFI were prolonged severe neutropenia ( $p = .05$ ) and having received tacrolimus ( $p = .04$ ). Antifungal therapy was successful in 7 of the 18 (39%) patients with breakthrough IFI and 8 of the 12 (67%) patients with non-breakthrough IFI,  $p = .13$ . Mortality at 12 weeks was 27%, 5 with breakthrough IFI and 3 with non-breakthrough IFI and was associated with prolonged severe neutropenia,  $p = .04$ .

**Conclusions** Patients with AML remain at risk for IFI despite the use of several different antifungal agents for prophylaxis. Mortality remains high in patients with AML who develop IFI.

**Keywords** Breakthrough invasive fungal infections · Mold infections · Acute leukemia · Antifungal prophylaxis · Aspergillosis

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## Introduction

Acute myeloid leukemia (AML) is associated with a high mortality rate, not just from the disease itself but also from opportunistic infections, including invasive fungal infections (IFIs). The use of fluconazole as prophylaxis led to a decrease in the incidence of invasive candidiasis, but mold infections remained a

problem [1, 2]. The development of mold-active agents, such as voriconazole and posaconazole, further decreased the incidence of IFI [3, 4]. However, breakthrough IFIs with both yeasts and molds continue to be reported among patients with AML who are receiving antifungal prophylaxis. In several series, breakthrough IFI among patients with AML has ranged from 1.2% to as high as 18% [5–10].

We studied a large cohort of patients who had AML, many of whom were receiving antifungal prophylaxis, in order to determine the occurrence of IFI, risk factors for developing IFI, the effect of exposure to prophylactic antifungal agents, and clinical outcomes at 12 weeks after initiation of appropriate antifungal therapy.

## Methods

### Patients and Setting

This was a single-center retrospective cohort study that included all patients  $\geq 18$  years of age who had AML and who were hospitalized from January 1, 2010, through December 31, 2013, at the University of Michigan Health System, a 1000-bed tertiary care center. Patients were selected and data retrieved by the Honest Broker Office at the University of Michigan. Each patient was followed for two years from entry into the study or until diagnosis of IFI, at which point they were followed for 12 weeks and then excluded from further analysis. Approval to perform this study was granted by the University of Michigan Medical Center Institutional Review Board.

During the study period, patients undergoing chemotherapy for AML typically did not receive antibacterial prophylaxis during initial induction therapy. With relapsed or refractory disease, patients with an absolute neutrophil count (ANC)  $\leq 1500/\mu\text{L}$  received oral levofloxacin until resolution of neutropenia and then again during subsequent episodes of neutropenia. Antifungal prophylaxis with fluconazole, voriconazole, or posaconazole was initiated when ANC fell to  $\leq 1500/\mu\text{L}$  and continued until resolution of neutropenia. Use of micafungin was indicated in patients receiving anthracycline derivatives due to high-risk drug–drug interactions with azoles [11]. Acyclovir was given throughout all chemotherapy cycles for antiviral prophylaxis. Patients receiving

purine analogue therapy received inhaled pentamidine monthly for *Pneumocystis* prophylaxis throughout all chemotherapy cycles, and this prophylaxis was continued for 6 months following the last dose of a purine analogue agent.

### Data Collection and Definitions

The electronic medical record was reviewed to obtain the following information: comorbidities, hematopoietic cell transplantation (HCT), antifungal prophylaxis, occurrence and type of IFI, and 12-week outcomes of patients with IFI. Data were entered and stored in a RedCap database.

Patients included in the study met the definitions for AML proposed by the European Leukemia Net [12]. Patients with acute promyelocytic leukemia were excluded from the study because of the distinctive treatment regimens used and the very low associated risk for IFI. The status of AML at the time IFI occurred was categorized as new diagnosis or if chemotherapy had been given, as response or failure, based on the response criteria proposed by the European Leukemia Net [11]. Prolonged severe neutropenia was defined as ANC  $\leq 500/\mu\text{L}$  for at least 10 days prior to an episode of IFI.

EORTC/MSG criteria were used for the definitions of proven, probable, and possible IFI [13]. *Pneumocystis jiroveci* pneumonia was considered a fungal infection and was defined as noted in the updated EORTC/MSG criteria [14]. Day of IFI was defined as the time when IFI was first suspected based on clinical, radiological, and/or microbiological findings. An IFI that was diagnosed after 7 days of starting or within 7 days of discontinuing an antifungal agent was considered to be a breakthrough IFI, even if the IFI was due to an organism outside the usual spectrum of activity of the antifungal drug to which the patient was exposed. Serum voriconazole and posaconazole trough levels were noted when available; reference range was 1.0–5.5  $\mu\text{g}/\text{mL}$  for voriconazole and  $> 700$  ng/mL for posaconazole.

Response to antifungal therapy and mortality in patients with IFI was assessed at 12 weeks after the initiation of appropriate antifungal therapy. Outcome of the IFI, based on previously published EORTC-MSG criteria, was recorded as success, which encompasses complete and partial responses, or failure,

which includes stable infection, progression of infection, and death [15].

### Statistical Analysis

Comparison of categorical variables was performed using chi-square or Fisher's exact test, and comparison of means was performed using ANOVA. Logistic regression was used to estimate associations of patient characteristics with development of breakthrough IFI and with 12-week survival. Statistical significance was defined as  $p$  value  $< 0.05$ . All statistical analyses were completed using SPSS software, version 26.0 (SPSS, Inc., Chicago, IL).

## Results

### Patients

A total of 333 patients with AML were included in the study. The mean age was  $59.1 \pm 16.1$  years, and 200 (60%) were men (Table 1). A total of 116 patients (35%) had received a HCT, of which 108 were allogeneic and 8 were umbilical cord blood. The most common comorbidities were diabetes, chronic pulmonary disease, and chronic kidney disease.

### Invasive Fungal Infections

Of the 333 patients, 98 had an IFI (29%), including 30 (9%) who had a proven or probable IFI (Table 2). There were 18 probable IFI and 13 proven IFI in 12 patients; one patient had proven concomitant infection with 2 different molds. A total of 68 patients had possible IFI based on radiographic and clinical criteria per EORTC/MSG definitions and were excluded from further analysis.

Of the 30 cases of proven and probable IFI, 24 (80%) (including one patient with concomitant aspergillosis and mucormycosis) were caused by molds, most commonly *Aspergillus* sp. ( $n = 17$ ) (Table 2). Of these 17, the diagnosis was established by a positive galactomannan assay from bronchoalveolar lavage fluid (BAL) in 11 and by culture in 6. Other molds causing IFI included Mucorales ( $n = 5$ ), *Alternaria alternata* ( $n = 2$ ), and *Scedosporium apiospermum* complex ( $n = 1$ ). Among the non-mold

**Table 1** Characteristics of 333 patients with acute myeloid leukemia

Patient characteristics	Number (%)
Age (mean $\pm$ SD)	$59.1 \pm 16.1$
Sex	
Male	200 (60)
Female	133 (40)
Comorbidities	
Diabetes mellitus	63 (19)
Chronic pulmonary disease	45 (13)
Chronic kidney disease	21 (6)
Alcohol abuse	6 (2)
Liver disease	3 (1)
Stem cell transplantation	116 (35)
Allogeneic stem cell	108 (32)
Umbilical cord blood	8 (2)
Graft vs host disease	75(22)
Immunosuppressive drugs	
Tacrolimus	88(26)
Mycophenolate mofetil	27 (8)
High dose corticosteroids <sup>a</sup>	71(21)
Invasive fungal infection	98 (29)
Possible	68 (20)
Probable	18 (5)
Proven	12(4)

<sup>a</sup>> 0.3 mg/kg/day prednisone equivalent for > 21 days

infections, 4 were invasive *Candida* infections and 2 were *Pneumocystis jiroveci* pneumonias.

Among the 30 proven or probable IFI episodes, 12 occurred in patients who were not receiving antifungal prophylaxis at the time of the diagnosis of IFI. Five of these patients developed an IFI less than 7 days after admission for induction chemotherapy; 4 were not neutropenic; 2 had not received *Pneumocystis* prophylaxis; and 1 had interrupted prophylaxis due to drug–drug interactions. The organisms causing infection in these patients were *Aspergillus* species ( $n = 6$ ), Mucorales ( $n = 3$ ), *P. jiroveci* ( $n = 2$ ), *A. alternata* ( $n = 1$ ), and *Candida glabrata* ( $n = 1$ ) (Table 2).

### Breakthrough Invasive Fungal Infections

Among the 30 proven and probable IFI, 18 (60%) were breakthrough IFI. All breakthrough IFI occurred in patients who were receiving antifungal agents for

**Table 2** Description of 30 proven/probable invasive fungal infections (IFIs)

Organism	Site of IFI	Type of IFI	Number
Breakthrough IFI			
<i>Aspergillus</i> spp	Pulmonary <sup>a</sup>	Probable	11
Mucorales	Pulmonary	Probable <sup>b</sup>	1
	Pulmonary/sinus	Proven <sup>c</sup>	1
<i>Alternaria alternata</i>	Pulmonary/sinus	Proven	1
<i>Scedosporium apiospermum</i> complex	Disseminated	Proven	1
<i>Candida krusei</i>	Bloodstream	Proven	2
<i>Candida famata</i>	Bloodstream	Proven	1
Non-breakthrough IFI <sup>d</sup>			
<i>Aspergillus</i> spp	Pulmonary <sup>e</sup>	Probable	3
	Sinus	Probable	1
		Proven	1
	Vertebra	Proven	1
Mucorales	Disseminated	Proven <sup>f</sup>	3
<i>Pneumocystis jirovecii</i>	Pulmonary	Probable	2
<i>Alternaria alternata</i>	Disseminated	Proven	1
<i>Candida glabrata</i>	Prostate abscess	Proven	1

<sup>a</sup>Nine of 11 breakthrough probable invasive pulmonary aspergillosis cases were diagnosed by non-culture-based testing and radiological findings

<sup>b</sup>*Rhizopus* spp

<sup>c</sup>*Mucor* spp

<sup>d</sup>One patient had concomitant proven mold infection due to *Aspergillus flavus* (sinus) and *Mucor* spp (disseminated) in non-breakthrough group

<sup>e</sup>Two of 3 non-breakthrough probable invasive pulmonary aspergillosis cases were diagnosed by non-culture-based testing and radiological findings

<sup>f</sup>One of 3 was due to *Rhizopus* spp; two were not identified to the genus level

prophylaxis; no breakthrough IFI occurred in patients who were receiving antifungal therapy for a documented IFI. The organisms causing infection among 18 patients receiving antifungal prophylaxis were *Aspergillus* sp. ( $n = 11$ ), Mucorales ( $n = 2$ ), *A. alternata* ( $n = 1$ ), *S. apiospermum* complex ( $n = 1$ ), *C. krusei* ( $n = 2$ ), and *C. famata* ( $n = 1$ ) (Table 2).

Breakthrough IFIs occurred with all prophylactic regimens (Table 3). Five patients taking micafungin developed aspergillosis ( $n = 4$ ) and scedosporiosis ( $n = 1$ ). Breakthrough invasive aspergillosis ( $n = 3$ ) and candidemia ( $n = 1$ ) occurred in patients receiving fluconazole. Among 4 patients who were receiving posaconazole suspension, 3 developed breakthrough infections with *Aspergillus* sp., and another with *A. alternata*. The patient who received prophylaxis with posaconazole tablets and had a serum trough

concentration > 1000 ng/mL developed a resistant *C. famata* infection. Four patients who received voriconazole, 3 of whom had therapeutic serum trough levels from 1.5 to 3.2 µg/mL, developed mucormycosis ( $n = 2$ ), aspergillosis ( $n = 1$ ), and candidemia ( $n = 1$ ).

Development of breakthrough IFI was significantly associated with prolonged severe neutropenia at the time of diagnosis ( $p = 0.05$ ) and having received oral tacrolimus ( $p = 0.04$ ) (Table 4). Binary logistic regression analysis revealed no independent predictor for breakthrough IFI.

## Outcomes

Antifungal therapy was deemed successful at 12 weeks in 15 of the 30 patients (50%) with a proven

**Table 3** Description of 18 breakthrough invasive fungal infections (bIFIs) in patients with acute myeloid leukemia (AML)

Age/ gender	AML status at time of b-IFI	Antifungal prophylaxis	Type and site of IFI	12-week outcome of IFI
22 F	Response	Micafungin	Probable pulmonary aspergillosis	Success (partial response)
37 F	Treatment failure	Micafungin	Probable pulmonary aspergillosis	Failure (death)
57 M	Response	Micafungin	Proven disseminated <i>Scedosporium apiospermum</i> infection	Failure (death)
64 M	Treatment failure	Micafungin	Probable pulmonary aspergillosis	Failure (stable response)
67 M	Response	Micafungin	Probable pulmonary aspergillosis	Success (complete response)
59 M	New diagnosis	Fluconazole	Probable pulmonary aspergillosis	Success (partial response)
46 F	Treatment failure	Fluconazole	Proven <i>Candida krusei</i> bloodstream infection	Success (complete response)
29 F	Response	Fluconazole	Probable pulmonary aspergillosis	Success (complete response)
52 M	Relapse	Fluconazole	Probable pulmonary aspergillosis	Failure (progression of disease)
63 F	Relapse	Posaconazole <sup>a</sup>	Proven <i>Alternaria alternata</i> pneumonia and sinusitis	Success (partial response)
51 M	Relapse	Posaconazole <sup>a</sup>	Probable pulmonary aspergillosis	Failure(death)
61 M	New diagnosis	Posaconazole <sup>a</sup>	Probable pulmonary aspergillosis	Success (complete response)
62 M	Treatment failure	Posaconazole <sup>a</sup>	Probable pulmonary aspergillosis	Failure (death)
53 M	Treatment failure	Posaconazole <sup>b</sup>	Proven <i>Candida famata</i> bloodstream infection	Failure (death)
75 M	Relapse	Voriconazole	Proven <i>Mucor spp</i> pneumonia and sinusitis	Failure (stable response)
69 M	Treatment failure	Voriconazole	Probable <i>Rhizopus spp</i> pneumonia	Failure (progression of disease)
36 M	Treatment failure	Voriconazole	Proven <i>Candida krusei</i> bloodstream infection	Failure (progression of disease)
30 M	New diagnosis	Voriconazole	Probable pulmonary aspergillosis	Failure (progression of disease)

<sup>a</sup> patients received oral posaconazole suspension, <sup>b</sup>patient received posaconazole extended release tablets

or probable IFI. Seven of 18 patients (39%) with breakthrough IFI had a successful response to anti-fungal therapy compared with 8 of 12 patients (67%) with non-breakthrough IFI,  $p = 0.13$ . The 4 failures in the non-breakthrough group were due to Mucorales ( $n = 2$ ), *Aspergillus* sp. ( $n = 1$ ), and *C. glabrata* ( $n = 1$ ). Mortality at 12 weeks in patients who developed an IFI was 27%; death occurred in 5 patients in the breakthrough IFI group and 3 patients in the non-breakthrough IFI group  $p = 0.60$ . By binary logistic regression, prolonged severe neutropenia at the time of IFI diagnosis was a significant risk factor for fatal

outcome at 12 weeks among patients with IFI,  $p = 0.04$ .

## Discussion

Over a 2-year period, we found that 29% of our patients with AML developed a proven, probable, or possible IFI. It is likely that some of the 68 (20%) patients with the diagnosis of a possible IFI, in fact, had another infection or a non-infectious disease, so they were excluded from our analysis. A total of 30 patients (9%) had proven or probable IFI, and 18 (5%)

**Table 4** Comparison of breakthrough invasive fungal infections (bIFIs) and non-breakthrough invasive fungal infections (non-bIFIs) in patients with acute myeloid leukemia

Patients characteristics	bIFI ( <i>n</i> = 18) number (%)	non-bIFI ( <i>n</i> = 12) number (%)	<i>P</i> value
Age (Mean ± SD)	60.2 ± 17.1	51.8 ± 15.3	0.17
<i>Sex</i>			
Male	13 (72)	9 (75)	0.6
<i>Status of AML time of IFI</i>			
New diagnosis <sup>a</sup>	3 (17)	5 (42)	0.14
Response	4 (22)	3 (25)	0.59
Treatment failure	7 (39)	4 (33)	0.53
Relapse	4 (22)	0	0.11
<i>Comorbidities</i>			
Diabetes mellitus	2 (11)	3 (25)	0.3
Chronic pulmonary disease	2 (11)	3 (25)	0.65
Chronic kidney disease	2 (11)	1 (8)	0.15
Mucositis	6 (33)	5 (42)	0.46
<i>Clostridium difficile</i> infection	2 (11)	2 (25)	0.3
Bacteremia	9 (50)	7 (58)	0.47
Intensive care unit admission	7 (39)	2 (17)	0.18
Prolonged severe neutropenia	11 (61)	3 (25)	0.05
<i>Stem cell transplantation</i>			
Allogeneic	8 (44)	2 (17)	0.12
Umbilical cord blood	1 (5)	0	0.6
Graft vs host disease	6 (33)	2	0.28
<i>Immunosuppressive drugs</i>			
Tacrolimus	8 (44)	1 (8)	0.04
Mycophenolate mofetil	3 (17)	1 (8)	0.47
High dose corticosteroids <sup>b</sup>	7 (39)	3 (25)	0.35

<sup>a</sup>These patients developed IFI in the setting of first remission induction chemotherapy for the treatment of newly diagnosed AML before a response to chemotherapy was documented

<sup>b</sup>> 0.3 mg/kg/day prednisone equivalent for > 21 days

of these 30 had proven or probable IFI in spite of the use of prophylactic antifungal agents. This rate of development of IFI while on prophylaxis is similar to that noted by others [7–10].

Prolonged neutropenia was associated with the development of breakthrough IFI and was found to be the only independent predictor of poor outcome in the entire cohort. This is similar to findings from other studies of patients with AML and those who have received a HCT [6, 7, 16, 17].

The most common IFI was invasive pulmonary aspergillosis, irrespective of whether antifungal prophylaxis was used and which specific agent was used. It is not unusual to have 3 cases of invasive

aspergillosis among patients receiving fluconazole prophylaxis, but it was striking that there were just as many patients with this IFI among those receiving prophylaxis with micafungin and posaconazole. Both of these agents are approved for prophylaxis in patients with acute leukemia and/or HCT [18–20].

Micafungin is better tolerated by many patients than the azoles, does not have the drug–drug interactions that preclude the use of azoles for some patients with AML, and is approved for prophylaxis in HCT recipients. However, the dose for prophylaxis, which is approved by the Food and Drug Administration only for yeast infections, is 50 mg daily, and this is unlikely to be effective for preventing aspergillosis [17].

Breakthrough infections with both *Candida* species and molds have been reported with echinocandin therapy [8, 21–23].

The most likely explanation for the failure of posaconazole to prevent invasive aspergillosis is the poor absorption of the oral suspension, which was used in 4 of the 5 patients who had breakthrough IFI [24, 25]. Therapeutic drug monitoring was not performed for 3 of these patients, and the fourth had a sub-therapeutic serum concentration. It is likely that serum concentrations were below those needed to prevent breakthrough IFI in these patients. Introduction of the posaconazole extended release oral tablet allows reliable absorption of this agent for most patients. However, several centers have reported breakthrough IFI in patients taking either posaconazole formulation and with adequate serum concentrations of this drug, and we noted this in one patient [26, 27].

We observed breakthrough IFI due to Mucorales only in patients receiving voriconazole for prophylaxis, but we also noted 3 other IFI due to Mucorales in patients not receiving antifungal prophylaxis. Voriconazole prophylaxis has been implicated as a risk factor for breakthrough mucormycosis in some studies, but not in others, suggesting that the risk for this infection is most likely multifactorial [28].

Another reason for breakthrough IFI while on prophylactic antifungal agents is increasing drug resistance among yeasts and molds [29, 30]. We noted that 3 breakthrough IFIs in our patients were caused by *Candida* species with known resistance (*C. krusei*) or variable susceptibilities (*C. famata*) to many azole agents [30, 31]. We do not have susceptibility data for most of the organisms causing IFI to help explain the development of breakthrough infections; for many of our patients, the diagnosis of probable invasive pulmonary aspergillosis was made by a positive galactomannan assay and established radiological criteria, and cultures were not positive.

Our study showed an overall 12-week mortality of 27% among patients who developed an IFI. The poor outcome of patients with IFI could be explained by the inherent virulence associated with the specific pathogens involved, as well as the very important factor of profound immunosuppression in patients with AML.

The limitations of our study include its retrospective, single-center design and the relatively small sample size. The study was carried out from 2010 to

2013 and thus reflects clinical practice at that time; changes in practice, particularly the introduction of new formulations of azole agents, will impact both the risk for and the outcome of breakthrough IFI and should be studied.

In conclusion, IFIs remain a significant problem among patients with AML despite the use of antifungal prophylaxis. Profound myelosuppression was a significant risk factor for both the development of breakthrough IFI and poor outcomes.

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