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ORIGINAL RESEARCH

Health-care utilization and outcomes of patients at high risk of invasive fungal infection

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Purpose: The objectives of this study were to present trends in posaconazole use over time and describe selected outcomes among patients at high risk of invasive fungal infections (IFIs) by use and type of antifungal medicine.

Methods: A retrospective observational study using data from the Premier Healthcare Database between January 2007 and March 2016 was conducted. Inpatient use of posaconazole by formulation and year is described. Separately, four cohorts of patients at high risk of IFI – those with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), hematopoietic stem-cell transplantation (HSCT), and graft-vs-host disease (GVHD) – but without a diagnosis code for IFI during the index encounter were identified as potential candidates for antifungal prophylaxis. Use of antifungal medication(s) in these patients was categorized. Index length of stay (LOS), index hospital costs, and subsequent inpatient and outpatient encounters with IFI at 30, 60, and 90 days post-index encounter are presented by antifungal group for each cohort. The percentage of patients with inpatient and outpatient encounters with IFI at 90 days post-index encounter was determined for each cohort by year.

Results: Use of posaconazole oral suspension increased through 2012, then declined as the tablet formulation became available in 2013. A total of 19,872 AML patients, 12,125 MDS patients, 14,220 HSCT patients, and 5,431 GVHD patients were considered potential candidates for antifungal prophylaxis; however, a large proportion of patients within each cohort (33%–94%) did not receive any antifungal drug during the index hospitalization. Index LOS, hospital costs, and subsequent encounters for IFI varied among cohorts and by antifungal group. Within each cohort, subsequent encounters for IFI at 90 days post-index encounter fluctuated but remained rare across different years.

Conclusion: Over time and as new posaconazole formulations became available, the frequency of use of each formulation changed. In addition, this study suggested a low rate of potential antifungal prophylaxis in high-risk patients. This is one of the first reports attempting to describe antifungal prophylaxis in a contemporary, large, all-payer, geographically representative hospital database.

Keywords: prophylaxis, acute myeloid leukemia, myelodysplastic syndromes, hematopoietic stem-cell transplantation, graft-vs-host disease, health-care outcomes

Introduction

Patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are at high risk for invasive fungal infection (IFI) when presented with prolonged neutropenia after induction chemotherapy.[1] IFI is associated with increased morbidity and mortality and is a serious concern in AML, MDS, and other immunocompromised

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patients, such as those undergoing hematopoietic stem-cell transplantation (HSCT) or with graft-vs-host disease (GVHD).[2,3] Several professional guidelines recommend using antifungal prophylaxis in high-risk patients and consider timely initiation of antifungal use as a critical component in improving patient outcomes.[4–6]

To date, many antifungal drugs have demonstrated poor efficacy, particularly in the prevention of invasive aspergillosis. The use of fluconazole as prophylaxis is limited by its narrower spectrum of antifungal activity, being effective only against *Candida* strains.[7] Voriconazole does not show any significantly greater benefit than other azoles in antifungal prophylaxis.[8–10] When given in capsules, itraconazole is absorbed poorly, and when given as oral suspension it has gastrointestinal side effects.[11] Micafungin and caspofungin can only be administered intravenously, are approved only for prophylaxis of *Candida* infections, and the effectiveness of prophylaxis in hematological patients has not been consistently reported.[12–15] Finally, unless there are contraindications to use of azole antifungals, amphotericin is not recommended for use as the primary prophylactic treatment.[16]

Posaconazole is a new-generation azole that is recommended for use in neutropenic patients, SCT recipients, and patients with severe GVHD for antifungal prophylaxis by National Comprehensive Cancer Network, American Society of Clinical Oncology, and Infectious Diseases Society of America guidelines.[5,7,17] Three formulations of posaconazole – oral suspension, delayed-release tablet, and parenteral – are currently US Food and Drug Administration (FDA)-approved for the prophylaxis of invasive *Aspergillus* and/or *Candida* infections. In clinical trials, posaconazole has proved to be clinically superior to other triazoles in preventing IFI, especially aspergillosis.[17,18] Implementation of clinical guidelines and research findings in current practice, however, has not been well followed. Further, real-world evidence leveraging nationwide, geographically representative data to assess associations between posaconazole use and patient outcomes is lacking.

This study set out to describe real-world use of different formulations of posaconazole in a hospital setting. Four cohorts of patients at high risk of IFI – those with AML, MDS, HSCT, and GVHD – and those without diagnosis codes for FI during the index hospitalization were identified as likely candidates for antifungal prophylaxis. Within each cohort, the observed antifungal use was identified and categorized as single (posaconazole or other antifungal), multiple (antifungals with and without posaconazole), or none. Selected economic and clinical outcomes are described for each of the cohorts.

Methods

Study design

A retrospective observational study using the Premier Healthcare Database (PHD) was conducted to describe real-world use of posaconazole in a hospital setting and among patients at high risk of FIs, as well as to explore use of common antifungal drugs and occurrence of IFIs up to 90 days after discharge.

Data source

The PHD is a large database of geographically diverse US hospitals containing patient- and hospital-level information and representing a variety of payer types. The PHD contains a subset of data from the Premier Quality Advisor platform that offers deidentified, Health Insurance Portability and Accountability Act-compliant data. Use of the PHD data for this study was considered exempt from institutional review-board oversight, as dictated by Title 45 Code of Federal Regulations (CFR), Part 46 of the US, specifically 45 CFR 46.101(b)(4) (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html). In addition, in accordance with the Health Insurance Portability and Accountability Act privacy rule, data disclosed from the PHD are considered deidentified as per 45 CFR 164.506(d)(2)(ii)(B) through the "expert determination" method.

During the study period, data from standard hospital-discharge files, including patient demographics, disease states, admission and discharge diagnoses, patient disposition, and discharge status were available from more than 654 million stays, representing more than 20% of all US hospital discharges. At the time of analyses, there were more than 151 million patients. The PHD also contains a date-stamped log of billed items, including procedures, devices, medications, laboratory tests, and diagnostic and therapeutic services at the individual patient level. Drug-utilization information is available by day of stay and includes quantity, dose, strength, and hospital cost. Patients can be tracked across inpatient and hospital-based outpatient settings, as well as across visits with a unique identifier within a single hospital. Hospital information included geographic location, population served (urban vs rural), teaching status, and number of beds.

Study population

All patients discharged from an inpatient hospital visit between January 1, 2007 and March 31, 2016 receiving at least one dose of posaconazole, whether used alone or in combination with other antifungals, were identified using medication-billing records in the PHD. The formulation used

(oral suspension, oral tablet, parenteral) was also identified from the billing records. Since the tablet formulation of posaconazole was approved by the FDA in November 2013 and the parenteral formulation approved in March 2014, any posaconazole used prior to November 2013 was labeled as the oral suspension. If the formulation after November 2013 could not be determined from the billing record, it was classified as an unknown formulation. Trends in use by formulation or use of combinations of posaconazole formulations were displayed over time.

AML patients that did not achieve remission or were in relapse and patients with MDS, HSCT, or GVHD were identified as high-risk population for IFIs and included in the study. For descriptions of antifungal-medication use in the study cohort, all patients discharged from an inpatient hospital visit between January 1, 2007 and March 31, 2016 with a primary diagnosis code for each condition were identified. A hierarchical approach was used to categorize patients into one of the four groups. All patients with a primary ICD9/10 diagnosis code for AML (205.00, 205.02, C92.00, C92.40, C92.50, C92.02, C92.42, or C92.52) who did not meet the criteria for HSCT were categorized into the AML cohort. All patients with a primary ICD9/10 diagnosis code for MDS (238.72-75, D46.0-2, D46.9 or D46.A-C) who did not meet the criteria for HSCT were categorized into the MDS cohort. Patients with a primary ICD9/10 procedure code for HSCT (Table S1) who did not meet the criteria for the GVHD cohort were categorized into the HSCT cohort. Patients with a primary or secondary ICD9/10 diagnosis code for GVHD (279.50-3 or D89.810-3) who also had at least one dose of a selected immunosuppressant drug (methylprednisolone, prednisone, beclomethasone, cyclosporine, sirolimus, tacrolimus, mycophenolate mofetil, thalidomide, methotrexate, azathioprine, pentostatin, infliximab, rituximab, etanercept, methoxsalen, denileukin, antithymocyte globulin, daclizumab, basiliximab, or alemtuzumab) on the hospital medication-billing record were categorized into the GVHD cohort.

For each cohort, the first qualifying visit was identified as the index visit. Patients were then excluded if they had an admission or discharge diagnosis code for an FI during the index visit (ICD9 diagnosis codes 112.XX, 114.X, 115.XX, 116.X, 117.X, 118, 348.89, 484.6, 484.7, 495.4, and 495.6; ICD10 diagnosis codes B36.8, B37.X-B49, H16.069, J67.4, and J67.6). Subsequent inpatient and outpatient encounters in the same hospital system were identified through 90 days after the index visit discharge date.

Antifungal-use groups of interest

Within each high-risk cohort, patients were further categorized into one of antifungal-use groups based upon the use of antifungal medications during the index visit:

- single antifungal (posaconazole) – the only antifungal used during the index visit was posaconazole
- single antifungal (not posaconazole) – use of only one of fluconazole, itraconazole, voriconazole, micafungin, caspofungin, or amphotericin B during the index visit
- multiple antifungals (including posaconazole) – multiple antifungal drugs listed above were used during index encounter, including posaconazole
- multiple antifungals (not including posaconazole) – multiple antifungal drugs used during the index visit, but none were posaconazole
- no antifungal – no antifungal drugs were used during the index visit

Patient and hospital characteristics

Selected patient and visit characteristics (age, sex, race, ethnicity, admission type, and discharge status) were obtained from the PHD and are presented by high-risk cohort and antifungal-treatment groups. Selected hospital characteristics (teaching status, urban/rural location, US Census geographical regions, and number of beds) were similarly obtained and are presented in the same manner.

Study outcomes

Outcomes of interest during the index hospitalization and following discharge from the index hospitalization were determined. Outcomes during index hospitalization were total hospital length of stay (LOS) and total hospital cost. Outcomes following index hospital discharge were the occurrence of 30-, 60-, and 90-day readmissions and subsequent outpatient visits with the presence of a primary or secondary ICD admission or discharge diagnosis code for IFI (Table S2).

Statistical analysis

Descriptive statistics were derived. Continuous data are expressed as means ± SD, minimum and maximum, and medians and IQR. Categorical data are expressed as counts and percentages. Patients with missing values for total hospital cost were excluded from cost analysis. Patients who died during the index encounter were excluded from the denominator for analyses of subsequent encounters.

Results

Posaconazole use in a hospital setting

Prior to 2013, the only formulation of posaconazole available in the US was the oral suspension. The number of patients receiving posaconazole oral suspension peaked in 2012 and rapidly declined thereafter (Figure 1). Much of that decline may have resulted from availability of the oral tablet formulation, which demonstrated rapid growth in use in 2014 and 2015. The proportion of inpatients receiving posaconazole who were administered the tablet formulation increased from 24.8% in 2014 to 62.3% in the first quarter of 2016 (data not shown), while the proportion of inpatients receiving the oral suspension decreased from 67.5% to 32.7% during this same period (data not shown). There was less use of the most recently marketed formulation: parenteral posaconazole. When used, it was frequently prescribed in combination with other formulations during the same hospitalization.

Patient and hospital characteristics of high-risk patients

Table 1 presents patient and hospital characteristics for each of the four patient cohorts. Table S3 presents patient and hospital characteristics by patient cohort for the five antifungal categories. A total of 51,648 patients who met study criteria

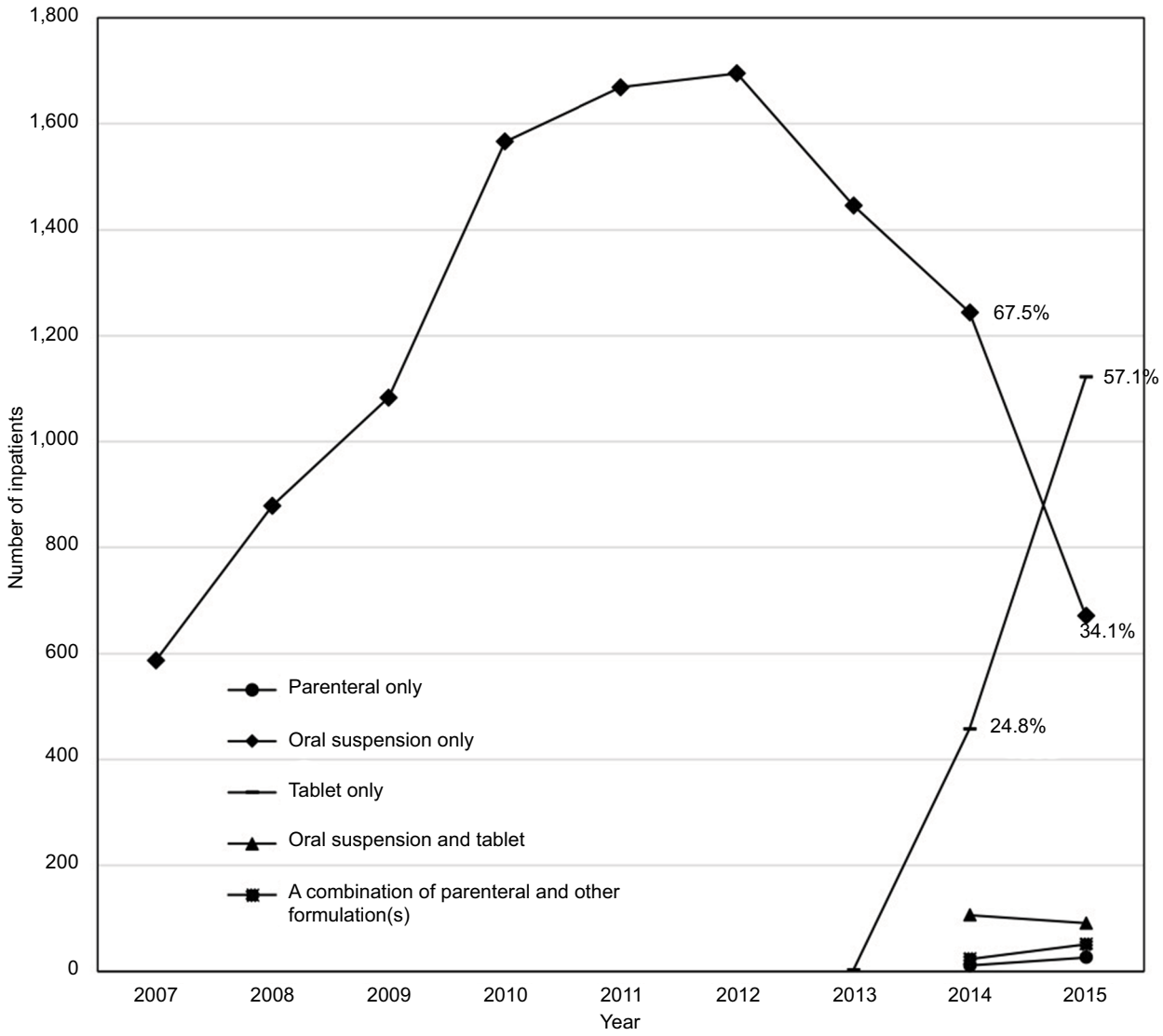

Figure 1 Inpatients receiving posaconazole by formulation and by year.

Notes: Patients receiving varying formulations of posaconazole during the study years. This graph highlights the declining number of inpatients with posaconazole oral suspension after 2013, when the oral tablet formulation became available. The proportion of inpatients receiving the tablet formulation has increased rapidly in recent years, and parenteral posaconazole was found to have a very small uptake. A total of nine cases from 2014 to the first quarter of 2016 had unknown or unidentifiable formulations.

Table 1 Patient, visit, and hospital characteristics of patients with a diagnosis of AML, MDS, HSCT, or GVHD without documented fungal infections

		AML		MDS		HSCT		GVHD	
Unique patients		19,872		12,125		14,220		5,431	
Unique providers		736		753		391		553	
Age, years	Minimum–maximum	0	85+	0	85+	0	85+	0	85+
	Mean	64		76		51		47	
	SD	±19.18		±12.75		±20.06		±18.71	
	Median	68		79		57		52	
	IQR	54	78	70	85	42	65	35	61
Age-group, years	0–17	562	2.8%	46	0.4%	1,495	10.5%	525	9.7%
	18–34	1,317	6.6%	89	0.7%	1,256	8.8%	787	14.5%
	35–44	1,253	6.3%	118	1.0%	1,133	8.0%	626	11.5%
	45–64	5,349	26.9%	1,576	13.0%	6,429	45.2%	2,627	48.4%
	65–74	4,770	24.0%	2,642	21.8%	3,233	22.7%	793	14.6%
	75+	6,621	33.3%	7,654	63.1%	674	4.7%	73	1.3%
Sex	Male	10,922	55.0%	6,628	54.7%	8,105	57.0%	3,139	57.8%
	Female	8,945	45.0%	5,495	45.3%	6,115	43.0%	2,292	42.2%
	Unknown	5	0.0%	2	0.0%	0	0.0%	0	0.0%
Race	White	14,209	71.5%	8,938	73.7%	10,030	70.5%	4,014	73.9%
	Black	1,917	9.6%	1,121	9.2%	1,632	11.5%	458	8.4%
	Other	3,746	18.9%	2,066	17.0%	2,558	18.0%	959	17.7%
Ethnicity	Not Hispanic or Latino	9,323	46.9%	5,805	47.9%	8,649	60.8%	3,196	58.8%
	Hispanic or Latino	1,234	6.2%	662	5.5%	967	6.8%	330	6.1%
	Other	9,315	46.9%	5,658	46.7%	4,604	32.4%	1,905	35.1%
Admission type	Urgent/emergent	16,765	84.4%	10,456	86.2%	5,143	36.2%	3,900	71.8%
	Elective	2,913	14.7%	1,572	13.0%	8,992	63.2%	1,460	26.9%
	Trauma	52	0.3%	23	0.2%	4	0.0%	15	0.3%
	Other/Unknown	142	0.7%	74	0.6%	81	0.6%	56	1.0%
Discharge status	Home	10,211	51.4%	8,241	68.0%	13,184	92.7%	4,092	75.3%
	Transferred	2,487	12.5%	335	2.8%	157	1.1%	482	8.9%
	SNF	877	4.4%	2,075	17.1%	322	2.3%	192	3.5%
	Expired	3,234	16.3%	541	4.5%	318	2.2%	405	7.5%
	Hospice	2,620	13.2%	814	6.7%	91	0.6%	95	1.7%
	Other/unknown	443	2.2%	119	1.0%	148	1.0%	165	3.0%
No. of beds	1–149	1,057	5.3%	1,087	9.0%	102	0.7%	223	4.1%
	150–249	2,366	11.9%	1,942	16.0%	1,577	11.1%	679	12.5%
	250–349	2,969	14.9%	2,312	19.1%	959	6.7%	604	11.1%
	350–449	3,372	17.0%	2,213	18.3%	1,299	9.1%	650	12.0%
	450–549	2,747	13.8%	1,685	13.9%	1,445	10.2%	481	8.9%
	550+	7,361	37.0%	2,886	23.8%	8,838	62.2%	2,794	51.4%
Geographic region	West	3,288	16.6%	1,921	15.8%	1,543	10.8%	778	14.3%
	Midwest	3,581	18.0%	2280	18.8%	2397	16.9%	835	15.4%
	Northeast	3,716	18.7%	2,425	20.0%	4,349	30.5%	1,436	26.4%
	South	9,287	46.7%	5499	45.4%	5931	41.7%	2382	43.8%
Teaching	Yes	9,405	47.3%	6,937	57.2%	3,733	26.3%	1,933	35.6%
	No	10,467	52.7%	5,188	42.8%	10,487	73.7%	3,498	64.4%
Urban/rural	Rural	1,350	6.8%	1,093	9.0%	396	2.8%	232	4.3%
	Urban	18,522	93.2%	11,032	91.0%	13,824	97.2%	5,199	95.7%

Note: All values are presented as number and percentages unless otherwise designated.
Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; HSCT, hematopoietic stem-cell transplantation; GVHD, graft-vs-host disease; SNF, skilled nursing facility.

were categorized: 19,872 (38%) AML patients, 12,125 (23%) MDS patients, 14,220 (28%) HSCT patients, and 5,431 (11%) GVHD patients (Table 1). Among these, 58% of AML patients (11,482), 94% of MDS patients (11,382), 33% of HSCT patients (4,736), and 37% of GVHD patients (2,014) did not receive any of the selected antifungal medications during the index hospitalization (Table S3). Posaconazole, alone or in combination with another drug, was received in <10% of patients across the four cohorts.

The median patient age was highest in the MDS cohort (median 79 years, IQR 70–85 years) and lowest in the GVHD cohort (median 52 years, IQR 35–61 years). In each cohort,

there was a higher proportion of men than women; however, in the subgroup of MDS patients receiving posaconazole plus other antifungals, only 41% were male. Across all four cohorts, approximately 70% of patients were white. Approximately 70%–85% of patients with AML, MDS, or GVHD had an emergent or urgent visit, while only 36% of patients with HSCT had an emergent or urgent visit. Most patients were discharged home, and there were more AML patients transferred to another hospital, hospice, or expired than other cohorts. Consistently across the four cohorts, it appeared that patients receiving posaconazole as the only antifungal during the index encounter had low in-hospital mortality among the five antifungal groups.

More than half of HSCT and GVHD patients were admitted to hospitals with 550+ beds, while fewer patients with AML (37%) or MDS (24%) were treated at such hospitals. With regard to geographical distribution, more patients with HSCT (30%) and GVHD (26%) were treated at hospitals in the Northeast than patients with AML (18%) or MDS (20%). Table S3 shows that patients treated with antifungals were more frequently seen in hospitals with 550+ beds than hospitals of smaller sizes. Posaconazole, alone or in combination with another antifungal, was found to be more frequently used in AML, MDS, and GVHD patients in the Northeast and in hospitals with 550+ beds, which is consistent with the fact that Northeast hospitals tend to have larger bed capacity than other regions in our study sample (data not shown).

The majority of patients with HSCT (73%) or GVHD (64%) were treated at teaching hospitals, whereas only around half of or fewer patients with AML (52%) or MDS (42%) were treated at teaching hospitals. Across all cohorts and treatment categories (Table S3), over 90% of patients were admitted to a hospital in an urban area. Overall, antifungal prophylaxis was more frequently given to all four cohorts by teaching hospitals. In both single and multiple antifungal therapies, posaconazole was more frequently given to AML and MDS patients by teaching hospitals.

Economic and clinical outcomes of high-risk patients

Tables 2–5 present economic and clinical outcomes by antifungal categories for AML, MDS, HSCT, and GVHD cohorts, respectively. Across these four cohorts, patients with no antifungal treatment were found to have the shortest LOS, whereas patients with more than one type of antifungal had the longest LOS. There was not a noticeable difference in LOS between patients treated with posaconazole only and patients treated with one other antifungal only or between patients receiving multiple antifungals treated with and without posaconazole. Consistently, in all four cohorts, patients with no antifungal treatment had the lowest total hospital cost, whereas patients with more than one type of antifungal had the highest. Total hospital costs were similar between patients treated with single antifungals whether posaconazole or other agent; and between patients receiving multiple antifungals whether with or without posaconazole.

IFI-related readmissions and subsequent outpatient visits were rare events. Figure 2 shows that the percentage of patients with subsequent inpatient and outpatient encounters with IFI at 90 days post-index encounter fluctuated yet remained very low over the study period. For each cohort, there was not a noticeable difference across different years. Patients with no antifungal treatment had the fewest IFI-related readmissions and subsequent outpatient visits, and no remarkable differences were found among the remaining four treatment groups (Tables 2–5).

Discussion

Antifungal prophylaxis for high-risk patients has been promoted by various scientific societies due to the rising incidence of life-threatening IFIs and undesired outcomes when initiation of antifungal use is delayed.[19] This is one of the first studies to observe and characterize the possible use of antifungal prophylaxis and associated outcomes in a large, representative database. Our findings indicate that across different cohorts of immunocompromised patients, antifungal prophylaxis appears to be underutilized, especially in patients with shorter hospital stays. As patient LOS extended, a greater proportion of the at-risk population started to receive multiple antifungal drugs, even when no FI was present. Although antifungal prophylaxis is currently regarded as the gold standard in situations with a high risk of FI, such as in these immunocompromised patients,[4,5,7,9] it is possible that the clinician's perspective of risk for an individual patient may vary and/or there may be inconsistency in the interpretation and application of guideline recommendations for antifungal prophylaxis.[20]

The unexpected finding that a substantial number of high-risk patients did not receive antifungal prophylaxis highlights the need for initiatives to promote the adoption of guideline recommendations. The higher proportion of patients receiving antifungal prophylaxis within teaching hospitals may indicate greater knowledge, receptivity, and/or availability of tools for utilization of antifungal prophylaxis or could be due to the fact that teaching hospitals may contain a higher proportion of complex patients considered at extremely high

Table 2 Economic and clinical outcomes in AML patients without fungal infection diagnosis

		Single antifungal (posaconazole)		Single antifungal (not posaconazole)		Multiple antifungals (including posaconazole)		Multiple antifungals (not including posaconazole)		No antifungal	
Unique patients		565		4,778		812		2,235		11,482	
Unique providers		103		516		112		309		724	
Denominator for index LOS and total index hospital cost		**n=565**		**n=4,778**		**n=812**		**n=2,235**		**n=11,482**	
Index LOS	Minimum–maximum	1	70	1	213	2	162	1	280	1	189
	Mean	24.79		20.63		35.22		34.01		7.02	
	SD	±13.79		±15.46		±18.39		±17.60		±8.56	
	Median	26		21		31		31		4	
	IQR	14	32	7	30	25	42	25	41	2	8
Total index hospital cost, USD$	Minimum–maximum	1,499.51	1,163,262	398.02	880,313	1419.57	4,535,851	3,225.15	964,870.3	1.09	977,379.8
	Mean	61,206.88		49,435.92		99,937.16		89,630.58		16,559.98	
	SD	±60,905.37		±45,897.58		±17,4345.8		±64,621.83		±24,928.34	
	Median	56,993.39		41,806.57		76,766.25		75,379.69		8,989.77	
	IQR	33,494.43	78,162.05	16,772.19	67,282.66	54,409.96	108,712.6	53,806.16	108,052.5	4,911.21	17,461.34
Denominator for readmissions and subsequent visits (excludes death during index visit)		**n=514**		**n=4,087**		**n=693**		**n=1,823**		**n=9,521**	
30-Day readmission with IFIs		3	0.6%	79	1.9%	10	1.4%	48	2.6%	88	0.9%
30-Day outpatient visit with IFIs		0	0	1	0	1	0.1%	2	0.1%	5	0.1%
60-Day readmission with IFIs		6	1.2%	117	2.9%	13	1.9%	84	4.6%	128	1.3%
60-Day outpatient visit with IFIs		0	0	6	0.1%	1	0.1%	6	0.3%	14	0.1%
90-Day readmission with IFIs		12	2.3%	153	3.7%	16	2.3%	109	6.0%	159	1.7%
90-Day outpatient visit with IFIs		0	0	7	0.2%	2	0.3%	9	0.5%	18	0.2%

Note: All values are presented as number and percentages unless otherwise designated.
Abbreviations: AML, acute myeloid leukemia; LOS, length of stay; IFIs, invasive fungal infections.

Table 3 Economic and clinical outcomes in MDS patients without fungal infection diagnosis

		Single antifungal (posaconazole)		Single antifungal (not posaconazole)		Multiple antifungals (including posaconazole)		Multiple antifungals (not including posaconazole)		No antifungal	
Unique patients		29		624		17		73		11,382	
Unique providers		19		300		10		56		748	
Denominator for index LOS and total index hospital cost		**n=29**		**n=624**		**n=17**		**n=73**		**n=11,382**	
Index LOS	Minimum–maximum	3	51	1	74	4	70	1	88	1	71
	Mean	11.59		10.07		31.59		20.97		4.76	
	SD	±11.36		±9.67		±18.57		±17.94		±4.54	
	Median	7		7		26		16		3	
	IQR	4	12	4	14	22	38	10	23	2	6
Total index hospital cost, USD$	Minimum–maximum	4,988.19	12,4338.3	613.72	311,336.4	15,860.76	321,775.3	5,540.52	443,352.4	6.24	223,411.4
	Mean	29,465.95		23,930.41		92,101.74		63,885.38		9,482.05	
	SD	±28,193.38		±29,116.92		±85,112.77		±78,483.42		±10,584.59	
	Median	16,912.13		14,973.61		61,276.62		38,536.14		65,40.84	
	IQR	12,977.8	30,012.21	7,238.77	29,733.78	37,403.97	110,684.9	19,868.83	76,730.25	3,804.16	11,252.56
Denominator for readmissions and subsequent visits (excludes death during index visit)		**n=27**		**n=560**		**n=17**		**n=55**		**n=10,925**	
30-Day readmission with IFIs		0	0	4	0.7%	2	11.8%	2	3.6%	56	0.5%
30-Day outpatient visit with IFIs		0	0	0	0	0	0	0	0	7	0.1%
60-Day readmission with IFIs		0	0	10	1.8%	2	11.8%	2	3.6%	96	0.9%
60-Day outpatient visit with IFIs		0	0	0	0	0	0	0	0	12	0.1%
90-Day readmission with IFIs		0	0	12	2.1%	2	11.8%	2	3.6%	128	1.2%
90-Day outpatient visit with IFIs		0	0	0	0	0	0	0	0	13	0.1%

Note: All values are presented as number and percentages unless otherwise designated.
Abbreviations: MDS, myelodysplastic syndrome; LOS, length of stay; IFIs, invasive fungal infections.

Table 4 Economic and clinical outcomes in HSCT patients without fungal infection diagnosis

		Single antifungal (posaconazole)		Single antifungal (not posaconazole)		Multiple antifungals (including posaconazole)		Multiple antifungals (not including posaconazole)		No antifungal	
Unique patients		109		7,513		228		1,634		4,736	
Unique providers		31		175		35		71		382	
Denominator for index LOS and total index hospital cost		**n=109**		**n=7,513**		**n=228**		**n=1,634**		**n=4,736**	
Index LOS	Minimum–maximum	2	60	1	203	2	122	5	309	1	121
	Mean	20.04		18.83		36.16		34.63		7.11	
	SD	±10.38		±9.94		±20.79		±22.12		±7.64	
	Median	20		18		29.5		28		4	
	IQR	16	26	14	22	23	42	23	38	3	8
Total index hospital cost, USD$	Minimum–maximum	4,734.8	317,707.6	254.08	3,406,753	7,147.45	584,183.1	13,850.58	1,839,113	37.71	392,230.4
	Mean	68,409.84		66,626.48		145,063.6		152,320.4		21,950.22	
	SD	±61,169.44		±70,213.10		±107,954.7		±130,782.9		±31,840.89	
	Median	55,097.42		49,135.52		110,882.4		117,352		11,553.08	
	IQR	35,831.58	80,799.15	35,054.09	77,012.63	65,179.02	192,504.7	69,234.34	194,578.4	6,542.26	21,294.55
Denominator for readmissions and subsequent visits (excludes death during index visit)		**n=108**		**n=7,451**		**n=203**		**n=1,484**		**n=4,656**	
30-Day readmission with IFIs		2	1.9%	38	0.5%	5	2.5%	26	1.8%	50	1.1%
30-Day outpatient visit with IFIs		0	0	6	0.1%	1	0.5%	3	0.2%	6	0.1%
60-Day readmission with IFIs		4	3.7%	63	0.8%	8	3.9%	33	2.2%	75	1.6%
60-Day outpatient visit with IFIs		0	0	9	0.1%	1	0.5%	5	0.3%	17	0.4%
90-Day readmission with IFIs		4	3.7%	77	1.0%	8	3.9%	38	2.6%	100	2.1%
90-Day outpatient visit with IFIs		1	0.9%	15	0.2%	1	0.5%	6	0.4%	21	0.5%

Note: All values are presented as number and percentages unless otherwise designated.
Abbreviations: HSCT, hematopoietic stem-cell transplantation; LOS, length of stay; IFIs, invasive fungal infections.

Table 5 Economic and clinical outcomes in GVHD patients without fungal infection diagnosis

		Single antifungal (posaconazole)		Single antifungal (not posaconazole)		Multiple antifungals (including posaconazole)		Multiple antifungals (not including posaconazole)		No antifungal	
Unique patients		225		2,192		231		769		2,014	
Unique providers		69		341		37		102		495	
Denominator for index LOS and total index hospital cost		**n=225**		**n=2,192**		**n=231**		**n=769**		**n=2,014**	
Index LOS	Minimum–maximum	1	55	1	196	3	184	1	255	1	197
	Mean	9.4		11.97		35.44		37.07		6.28	
	SD	±10.76		±16.14		±28.67		±31.53		±9.20	
	Median	5		6		29		31		4	
	IQR	3	11	3	15	19	46	16	47	2	7
Total index hospital cost, USD$	Minimum–maximum	1,157.65	288,145	924.71	1,691,789	5,416.78	767,010.5	2,235.59	2,154,246	95.79	675,867.5
	Mean	28,524.02		42,722.97		137,906.8		171,763.4		17,449.48	
	SD	±42,295.20		±81,534.22		±138,165.2		±189,478.3		±40,378.73	
	Median	12,373.78		14,671.42		96,129.21		125,417		8,489.03	
	IQR	7,400.29	31,269.96	7,151.84	42,652.34	47,203.79	178,955.9	45,862.75	220,542.7	4,529.42	16,350.46
Denominator for readmissions and subsequent visits (excludes death during index visit)		**n=218**		**n=2,062**		**n=197**		**n=624**		**n=1,925**	
30-Day readmission with IFIs		4	1.8%	32	1.6%	4	2.0%	24	3.8%	12	0.6%
30-Day outpatient visit with IFIs		1	0.5%	5	0.2%	2	1.0%	3	0.5%	2	0.1%
60-Day readmission with IFIs		8	3.7%	51	2.5%	7	3.6%	32	5.1%	23	1.2%
60-Day outpatient visit with IFIs		1	0.5%	8	0.4%	2	1.0%	4	0.6%	4	0.2%
90-Day readmission with IFIs		10	4.6%	65	3.2%	8	4.1%	38	6.1%	30	1.6%
90-Day outpatient visit with IFIs		1	0.5%	10	0.5%	3	1.5%	5	0.8%	7	0.4%

Note: All values are presented as number and percentages unless otherwise designated.
Abbreviations: GVHD, graft-vs-host disease; LOS, length of stay; IFIs, invasive fungal infections.

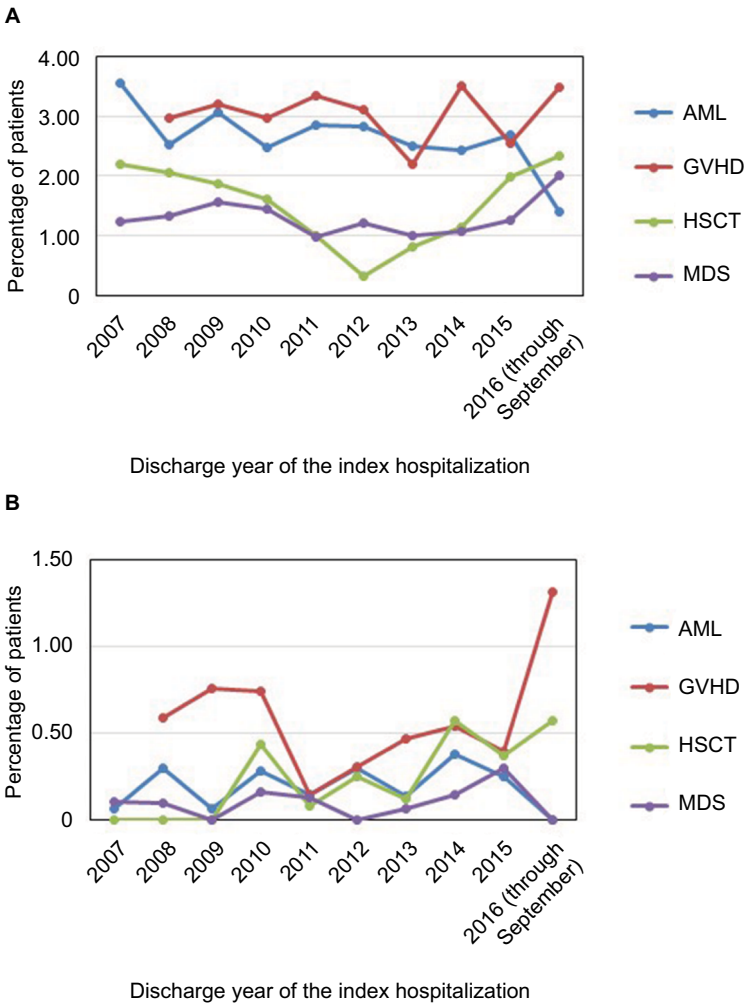

Figure 2 Inpatients with 90-day subsequent inpatient (**A**) and outpatient visits (**B**) with IFI by cohort and by year.
Notes: There was no noticeable trend over time, and patients with 90-day IFI-related subsequent inpatient and outpatient visits appeared to be rare across the four study cohorts. No GVHD encounters in 2007 met the study-inclusion criteria; therefore, readmissions and outpatient visits were not presented for the GVHD cohort in 2007.
Abbreviations: AML, acute myeloid leukemia; GVHD, graft-vs-host disease; HSCT, hematopoietic stem-cell transplantation; IFI, invasive fungal infection; MDS, myelodysplastic syndrome.

risk of FIs. Regional differences may also indicate varying degrees of knowledge, receptivity, and available resources. Additional investigations may facilitate a better understanding of clinician decision-making and guide development of tools for greater use of antifungal prophylaxis in appropriate patients across all hospitals in the nation.

There are a number of limitations to this study. First, the identification of antifungals was based on text-string searching in hospitals' charge masters. Since hospitals record their pharmacy costs in a variety of ways, some discharges that used an antifungal of interest may not have been captured. Second, due to the retrospective nature of this study and lack of access to medical records, it was extremely difficult to differentiate antifungal prophylaxis from treatment or empirical treatment. One important assumption of the study was that patients with antifungal use who did not have any diagnosis for an FI were likely receiving the antifungal(s) for prophylaxis. Under this assumption, those who received antifungal prophylaxis in the beginning of their stay but later developed an FI were not a focus of this study, and addition of this subset of patients in future studies could lead to different conclusions. Third, the risk of IFI and corresponding therapeutic strategies to address IFI were not constant during all the phases of treatment of the four cohorts. For example, since induction chemotherapy is the first time that a patient experiences profound immunosuppression, most AML patients are at greater risk of IFI at this stage, but differentiations of the treatment stage of each patient were not included in this study. Fourth, patients discharged from January 1, 2007 to March 30, 2007 may have had a hospitalization dur-

ing the 90 days prior to their index hospitalization, raising a possibility, albeit small, that some readmissions might be misclassified. It is also important to note that this US study may not be generalizable to other health-care settings. Lastly, the current study design was descriptive. No unadjusted or adjusted comparisons were made.

Conclusion

To date, there has been limited retrospective research using a large, all-payer, geographically representative hospital database to describe high-risk patients who require antifungal prophylaxis. This current study, despite its limitations, adds real-world knowledge to this field. The results revealed that contrary to guideline recommendations, some high-risk patients did not receive any antifungal prophylaxis. Additional research is necessary to confirm this finding and determine reasons for potential underutilization of antifungal prophylaxis in high-risk patients, in order to develop interventions and tools to improve guideline adherence and clinical outcomes.

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Disclosure

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Supplementary material

Table S1 Primary ICD9/10 procedure code for hematopoietic stem-cell transplantation

ICD9: 41.0X
ICD10: 30230AZ, 30230G0, 30230G1, 30230X0, 30230X1, 30230Y0, 30230Y1, 30233AZ, 30233G0, 30233G1, 30233X0, 30233X1, 30233Y0, 30233Y1, 30240AZ, 30240G0, 30240G1, 30240X0, 30240X1, 30240Y0, 30240Y1, 30243AZ, 30243G0, 30243G1, 30243X0, 30243X1, 30243Y0, 30243Y1, 30250G0, 30250G1, 30250X0, 30250X1, 30250Y0, 30250Y1, 30253G0, 30253G1, 30253X0, 30253X1, 30253Y0, 30253Y1, 30260G0, 30260G1, 30260X0, 30260X1, 30260Y0, 30260Y1, 30263G0, 30263G1, 30263X0, 30263X1, 30263Y0, 30263Y1, 3E03005, 3E03305, 3E04005, 3E04305, 3E05005, 3E05305, 3E06005, or 3E06305

Table S2 Primary or secondary ICD admission or discharge diagnosis code for invasive fungal infection

ICD9: 112.2, 112.4, 112.5, 112.81, 112.83, 112.84, 112.85, 112.89, 112.9, 114, 114.1, 114.2, 114.3, 114.4, 114.5, 114.9, 115, 115.01, 115.02, 115.03, 115.04, 115.05, 115.09, 115.11, 115.12, 115.13, 115.14, 115.15, 115.19, 115.91, 115.92, 115.93, 115.94, 115.95, 115.99, 116, 116.1, 117.1, 117.2, 117.3, 117.5, 117.6, 117.7, 117.8, 117.9, 118, 348.89, 484.6, 484.7, 495.4 or 495.6
ICD-10: B37.1, B37.41, B37.49, B37.5, B37.6, B37.7, B37.81, B37.82, B37.89, B37.9, B38.0, B38.1, B38.2, B38.4, B38.7, B38.81, B38.89, B38.9, B39.0, B39.1, B39.2, B39.3, B39.4, B39.5, B39.9, B40.0, B40.1, B40.2, B40.7, B40.81, B40.89, B40.9, B41.0, B41.7, B41.8, B41.9, B42.0, B42.1, B42.7, B42.81, B42.89, B42.9, B43.1, B43.2, B43.8, B43.9, B44.0, B44.1, B44.7, B44.81, B44.89, B44.9, B45.0, B45.1, B45.3, B45.7, B45.8, B45.9, B46.0, B46.1, B46.2, B46.4, B46.5, B46.8, B46.9, B47.0, B47.1, B48.2, B48.3, B48.4, B48.8, B49, G93.89, H16.069, J67.4 or J67.6

Table S3 Patient, visit, and hospital characteristics by antifungal use

AML		Single antifungal (posaconazole)		Single antifungal (not posaconazole)		Multiple antifungals (including posaconazole)		Multiple antifungals (not including posaconazole)		No antifungal	
Unique patients		565		4,778		812		2,235		11,482	
Unique providers		103		516		112		309		724	
Age, years	Minimum–maximum	0	85+	0	85+	5	85+	0	85+	0	85+
	Mean	57		58		56		54		69	
	SD	±16.35		±19.88		±15.52		±18.33		±17.72	
	Median	60		63		59		58		73	
	IQR	47	69	48	73	45	68	44	67	61	81
Age-group, years	0–17	9	1.6%	246	5.1%	4	0.5%	118	5.3%	185	1.6%
	18–34	51	9.0%	397	8.3%	91	11.2%	243	10.9%	535	4.7%
	35–44	66	11.7%	373	7.8%	96	11.8%	208	9.3%	510	4.4%
	45–64	231	40.9%	1,571	32.9%	353	43.5%	940	42.1%	2,254	19.6%
	65–74	134	23.7%	1,189	24.9%	195	24.0%	531	23.8%	2,721	23.7%
	75+	74	13.1%	1,002	21.0%	73	9.0%	195	8.7%	5,277	46.0%
Sex	Male	334	59.1%	2,662	55.7%	398	49.0%	1,191	53.3%	6,337	55.2%
	Female	231	40.9%	2,115	44.3%	414	51.0%	1,042	46.6%	5,143	44.8%
	Unknown	0	0	1	0	0	0	2	0.1%	2	0
Race	White	398	70.4%	3,327	69.6%	600	73.9%	1,517	67.9%	8,367	72.9%
	Black	46	8.1%	469	9.8%	77	9.5%	237	10.6%	1,088	9.5%
	Other	121	21.4%	982	20.6%	135	16.6%	481	21.5%	2,027	17.7%
Ethnicity	Not Hispanic or Latino	310	54.9%	2,139	44.8%	459	56.5%	1,036	46.4%	5,379	46.8%
	Hispanic or Latino	52	9.2%	348	7.3%	56	6.9%	159	7.1%	619	5.4%
	Other	203	35.9%	2,291	47.9%	297	36.6%	1,040	46.5%	5,484	47.8%
Admission type	Urgent/emergent	464	82.1%	3,896	81.5%	639	78.7%	1,840	82.3%	9,926	86.4%
	Elective	91	16.1%	847	17.7%	151	18.6%	375	16.8%	1,449	12.6%
	Trauma	0	0	13	0.3%	1	0.1%	8	0.4%	30	0.3%
	Other/unknown	10	1.8%	22	0.5%	21	2.6%	12	0.5%	77	0.7%

(*Continued*)

Table S3 (*Continued*)

AML		Single antifungal (posaconazole)		Single antifungal (not posaconazole)		Multiple antifungals (including posaconazole)		Multiple antifungals (not including posaconazole)		No antifungal	
Discharge status	Home	440	77.9%	3,093	64.7%	592	72.9%	1,480	66.2%	4,606	40.1%
	Transferred	19	3.4%	356	7.5%	28	3.4%	105	4.7%	1,979	17.2%
	SNF	15	2.7%	166	3.5%	27	3.3%	75	3.4%	594	5.2%
	Expired	51	9.0%	691	14.5%	119	14.7%	412	18.4%	1,961	17.1%
	Hospice	31	5.5%	393	8.2%	33	4.1%	138	6.2%	2,025	17.6%
	Other/unknown	9	1.6%	79	1.7%	13	1.6%	25	1.1%	317	2.8%
No. of beds	1–149	2	0.4%	140	2.9%	1	0.1%	29	1.3%	885	7.7%
	150–249	7	1.2%	492	10.3%	37	4.6%	229	10.2%	1,601	13.9%
	250–349	60	10.6%	625	13.1%	104	12.8%	220	9.8%	1,960	17.1%
	350–449	119	21.1%	661	13.8%	134	16.5%	255	11.4%	2,203	19.2%
	450–549	34	6.0%	738	15.4%	36	4.4%	324	14.5%	1,615	14.1%
	550+	343	60.7%	2,122	44.4%	500	61.6%	1,178	52.7%	3,218	28.0%
Geographic region	West	44	7.7%	807	16.9%	53	6.5%	338	15.1%	2,046	17.8%
	Midwest	55	9.8%	737	15.5%	87	10.7%	372	16.7%	2,330	20.3%
	Northeast	183	32.4%	817	17.1%	196	24.1%	405	18.2%	2,115	18.4%
	South	283	50.1%	2417	50.7%	476	58.7%	1120	50.2%	4,991	43.5%
Teaching	Yes	156	27.6%	2,133	44.6%	187	23.0%	819	36.6%	6,110	53.2%
	No	409	72.4%	2,645	55.4%	625	77.0%	1,416	63.4%	5,372	46.8%
Urban/rural	Rural	6	1.1%	244	5.1%	11	1.4%	82	3.7%	1,007	8.8%
	Urban	559	98.9%	4,534	94.9%	801	98.6%	2,153	96.3%	10,475	91.2%
MDS											
Unique patients		29		624		17		73		11,382	
Unique providers		19		300		10		56		748	
Age, years	Minimum–maximum	20	85	0	85+	6	81	1	85+	0	85+
	Mean	62		68		57		65		77	
	SD	±15.31		±14.99		±19.28		±13.64		±12.36	
	Median	68		71		62		66		79	
	IQR	53	73	61	79	51	68	58	73	71	86
Age-group, years	0–17	0	0	5	0.8%	1	5.9%	1	1.4%	39	0.3%
	18–34	2	6.9%	22	3.5%	1	5.9%	1	1.4%	63	0.6%
	35–44	2	6.9%	13	2.1%	0	0	2	2.7%	101	0.9%
	45–64	8	27.6%	162	26.0%	9	52.9%	29	39.7%	1,368	12.0%
	65–74	13	44.8%	172	27.6%	3	17.6%	23	31.5%	2,431	21.4%
	75+	4	13.8%	250	40.1%	3	17.6%	17	23.3%	7,380	64.8%
Sex	Male	21	72.4%	377	60.4%	7	41.2%	36	49.3%	6,187	54.4%
	Female	8	27.6%	246	39.4%	10	58.8%	37	50.7%	5,194	45.6%
	Unknown	0	0	1	0.2%	0	0	0	0	1	0
Race	White	18	62.1%	453	72.6%	12	70.6%	54	74.0%	8,401	73.8%
	Black	5	17.2%	57	9.1%	2	11.8%	7	9.6%	1,050	9.2%
	Other	6	20.7%	114	18.3%	3	17.6%	12	16.4%	1,931	17.0%
Ethnicity	Not Hispanic or Latino	17	58.6%	295	47.3%	11	64.7%	41	56.2%	5,441	47.8%
	Hispanic or Latino	3	10.3%	44	7.1%	1	5.9%	2	2.7%	612	5.4%
	Other	9	31.0%	285	45.7%	5	29.4%	30	41.1%	5,329	46.8%
Admission type	Urgent/emergent	18	62.1%	510	81.7%	13	76.5%	58	79.4%	9,857	86.6%
	Elective	11	37.9%	109	17.5%	4	23.5%	14	19.2%	1,434	12.6%
	Trauma	0	0	1	0.2%	0	0	1	1.4%	21	0.2%
	Other/unknown	0	0	4	0.6%	0	0	0	0	70	0.6%
Discharge status	Home	25	86.2%	399	63.9%	14	82.4%	28	38.4%	7,775	68.3%
	Transferred	0	0	25	4.0%	1	5.9%	8	11.0%	301	2.6%
	SNF	0	0	70	11.2%	1	5.9%	8	11.0%	1,996	17.5%
	Expired	2	6.9%	64	10.3%	0	0	18	24.7%	457	4.0%
	Hospice	1	3.4%	57	9.1%	1	5.9%	11	15.1%	744	6.5%
	Other/unknown	1	3.4%	9	1.4%	0	0	0	0	109	1.0%

(*Continued*)

Table S3 (*Continued*)

AML		Single antifungal (posaconazole)		Single antifungal (not posaconazole)		Multiple antifungals (including posaconazole)		Multiple antifungals (not including posaconazole)		No antifungal	
No. of beds	1–149	0	0	32	5.1%	0	0	2	2.7%	1,053	9.3%
	150–249	1	3.4%	85	13.6%	1	5.9%	9	12.3%	1,846	16.2%
	250–349	4	13.8%	112	17.9%	1	5.9%	8	11.0%	2,187	19.2%
	350–449	4	13.8%	99	15.9%	3	17.6%	10	13.7%	2,097	18.4%
	450–549	1	3.4%	103	16.5%	1	5.9%	16	21.9%	1,564	13.7%
	550+	19	65.5%	193	30.9%	11	64.7%	28	38.4%	2,635	23.2%
Geographic region	West	3	10.3%	94	15.1%	1	5.9%	10	13.7%	1,813	15.9%
	Midwest	2	6.9%	75	12.0%	2	11.8%	9	12.3%	2,192	19.3%
	Northeast	10	34.5%	110	17.6%	4	23.5%	12	16.4%	2,289	20.1%
	South	14	48.2%	345	55.3%	10	58.9%	42	57.6%	5,088	44.7%
Teaching	Yes	9	31.0%	338	54.2%	3	17.6%	30	41.1%	6,557	57.6%
	No	20	69.0%	286	45.8%	14	82.4%	43	58.9%	4,825	42.4%
Urban/rural	Rural	0	0	48	7.7%	0	0	6	8.2%	1,039	9.1%
	Urban	29	100%	576	92.3%	17	100%	67	91.8%	10,343	90.9%
HSCT											
Unique patients		109		7,513		228		1,634		4,736	
Unique providers		31		175		35		71		382	
Age, years	Minimum–maximum	1	85+	0	85+	4	82	0	85	0	85+
	Mean	53		53		52		43		51	
	SD	±16.48		±17.52		±15.63		±22.28		±22.48	
	Median	57		58		55		51		57	
	IQR	46	64	46	65	44.5	63	24	61	38	67
Age-group, years	0–17	4	3.7%	470	6.3%	8	3.5%	326	20	687	14.5%
	18–34	13	11.9%	617	8.2%	28	12.3%	194	11.9%	404	8.5%
	35–44	8	7.3%	622	8.3%	21	9.2%	153	9.4%	329	6.9%
	45–64	59	54.1%	3,711	49.4%	121	53.1%	674	41.2%	1,864	39.4%
	65–74	19	17.4%	1,914	25.5%	46	20.2%	269	16.5%	985	20.8%
	75 +	6	5.5%	179	2.4%	4	1.8%	18	1.1%	467	9.9%
Sex	Male	63	57.8%	4,345	57.8%	138	60.5%	955	58.4%	2,604	55.0%
	Female	46	42.2%	3,168	42.2%	90	39.5%	679	41.6%	2,132	45.0%
	Unknown	0	0	0	0	0	0	0	0	0	0
Race	White	69	63.3%	5,359	71.3%	138	60.5%	1,034	63.3%	3,430	72.4%
	Black	6	5.5%	873	11.6%	18	7.9%	196	12.0%	539	11.4%
	Other	34	31.2%	1,281	17.1%	72	31.6%	404	24.7%	767	16.2%
Ethnicity	Not Hispanic or Latino	70	64.2%	4,354	58.0%	118	51.8%	819	50.1%	3,288	69.4%
	Hispanic or Latino	10	9.2%	482	6.4%	14	6.1%	111	6.8%	350	7.4%
	Other	29	26.6%	2,677	35.6%	96	42.1%	704	43.1%	1,098	23.2%
Admission type	Urgent/emergent	43	39.5%	2,352	31.3%	82	35.9%	508	31.1%	2,158	45.5%
	Elective	65	59.6%	5,117	68.1%	146	64.0%	1,113	68.1%	2,551	53.9%
	Trauma	0	0	2	0	0	0	1	0.1%	1	0
	Other/unknown	1	0.9%	42	0.6%	0	0	12	0.7%	26	0.5%
Discharge status	Home	107	98.2%	7,197	95.8%	194	85.1%	1,388	84.9%	4,298	90.8%
	Transferred	1	0.9%	53	0.7%	4	1.8%	32	2.0%	67	1.4%
	SNF	0	0	92	1.2%	0	0	27	1.7%	203	4.3%
	Expired	1	0.9%	62	0.8%	25	11.0%	150	9.2%	80	1.7%
	Hospice	0	0	17	0.2%	2	0.9%	14	0.9%	58	1.2%
	Other/unknown	0	0	92	1.2%	3	1.3%	23	1.4%	30	0.6%
No. of beds	1–149	0	0	12	0.2%	0	0	0	0	90	1.9%
	150–249	4	3.7%	833	11.1%	8	3.5%	202	12.4%	530	11.2%
	250–349	4	3.7%	421	5.6%	9	3.9%	65	4.0%	460	9.7%
	350–449	24	22.0%	477	6.3%	26	11.4%	69	4.2%	703	14.8%

(*Continued*)

Table S3 (*Continued*)

AML		Single antifungal (posaconazole)		Single antifungal (not posaconazole)		Multiple antifungals (including posaconazole)		Multiple antifungals (not including posaconazole)		No antifungal	
	450–549	5	4.6%	531	7.1%	8	3.5%	134	8.2%	767	16.2%
	550+	72	66.1%	5,239	69.7%	177	77.6%	1,164	71.2%	2,186	46.2%
Geographic region	West	10	9.2%	687	9.1%	9	3.9%	70	4.3%	767	16.2%
	Midwest	15	13.7%	1116	14.8%	24	10.5%	271	16.6%	971	20.5%
	Northeast	31	28.4%	2,740	36.5%	93	40.8%	630	38.6%	855	18.0%
	South	53	48.7%	2970	39.5%	102	44.7%	663	40.6%	2,143	45.3%
Teaching	Yes	28	25.7%	1,606	21.4%	24	10.5%	243	14.9%	1,832	38.7%
	No	81	74.3%	5,907	78.6%	204	89.5%	1,391	85.1%	2,904	61.3%
Urban/rural	Rural	0	0	143	1.9%	0	0	6	0.4%	247	5.2%
	Urban	109	100.0%	7,370	98.1%	228	100.0%	1,628	99.6%	4,489	94.8%
GVHD											
Unique patients		225		2,192		231		769		2,014	
Unique providers		69		341		37		102		495	
Age, years	Minimum–maximum	0	74	0	85	12	78	0	77	0	85+
	Mean	51		47		50		42		49	
	SD	±14.53		±18.86		±15.13		±21.12		±17.92	
	Median Age-group, years	55		52		53		48		53	
	IQR	42	62	36	61	42	62	24	59	37	62
Age-group, years	0–17	3	1.3%	230	10.5%	6	2.6%	143	18.6%	143	7.1%
	18–34	39	17.3%	289	13.2%	38	16.5%	124	16.1%	297	14.7%
	35–44	26	11.6%	250	11.4%	21	9.1%	84	10.9%	245	12.2%
	45–64	120	53.3%	1,085	49.5%	125	54.1%	320	41.6%	977	48.5%
	65–74	37	16.4%	323	14.7%	40	17.3%	95	12.4%	298	14.8%
	75+	0	0	15	0.7%	1	0.4%	3	0.4%	54	2.7%
Sex	Male	144	64.0%	1,268	57.8%	132	57.1%	451	58.6%	1,144	56.8%
	Female	81	36.0%	924	42.2%	99	42.9%	318	41.4%	870	43.2%
	Unknown	0	0	0	0	0	0	0	0	0	0
Race	White	181	80.4%	1,668	76.1%	156	67.5%	554	72.0%	1,455	72.2%
	Black	14	6.2%	146	6.7%	23	10.0%	73	9.5%	202	10.0%
	Other	30	13.3%	378	17.2%	52	22.5%	142	18.5%	357	17.7%
Ethnicity	Not Hispanic or Latino	157	69.8%	1,295	59.1%	148	64.1%	449	58.4%	1,147	57.0%
	Hispanic or Latino	17	7.6%	126	5.7%	11	4.8%	57	7.4%	119	5.9%
	Other	51	22.7%	771	35.2%	72	31.2%	263	34.2%	748	37.1%
Admission type	Urgent/emergent	179	79.6%	1,576	71.9%	140	60.6%	409	53.1%	1,596	79.2%
	Elective	45	20.0%	593	27.1%	89	38.5%	351	45.6%	382	19.0%
	Trauma	1	0.4%	5	0.2%	0	0	1	0.1%	8	0.4%
	Other/unknown	0	0	18	0.8%	2	0.9%	8	1.0%	28	1.4%
Discharge status	Home	186	82.7%	1,702	77.6%	160	69.3%	526	68.4%	1,518	75.4%
	Transferred	13	5.8%	201	9.2%	16	6.9%	53	6.9%	199	9.9%
	SNF	9	4.0%	55	2.5%	6	2.6%	16	2.1%	106	5.3%
	Expired	7	3.1%	130	5.9%	34	14.7%	145	18.9%	89	4.4%
	Hospice	3	1.3%	39	1.8%	9	3.9%	14	1.8%	30	1.5%
	Other/unknown	7	3.1%	65	3.0%	6	2.6%	15	2.0%	72	3.6%
No. of beds	1–149	2	0.9%	57	2.6%	1	0.4%	4	0.5%	159	7.9%
	150–249	10	4.4%	271	12.4%	9	3.9%	150	19.5%	239	11.9%
	250–349	12	5.3%	218	9.9%	12	5.2%	31	4.0%	331	16.4%
	350–449	19	8.4%	226	10.3%	9	3.9%	44	5.7%	352	17.5%
	450–549	20	8.9%	165	7.5%	9	3.9%	40	5.2%	247	12.3%
	550+	162	72.0%	1,255	57.3%	191	82.7%	500	65.0%	686	34.1%

(*Continued*)

Table S3 (*Continued*)

AML		Single antifungal (posaconazole)		Single antifungal (not posaconazole)		Multiple antifungals (including posaconazole)		Multiple antifungals (not including posaconazole)		No antifungal	
Geographic region	West	26	11.5%	271	12.3%	7	3.0%	42	5.5%	432	21.4%
	Midwest	24	10.6%	327	14.9%	12	5.2%	114	14.9%	358	17.8%
	Northeast	94	41.8%	574	26.2%	118	51.1%	268	34.8%	382	19.0%
	South	81	36.0%	1020	46.5%	94	40.7%	345	44.9%	842	41.8%
Teaching	Yes	42	18.7%	743	33.9%	16	6.9%	203	26.4%	929	46.1%
	No	183	81.3%	1,449	66.1%	215	93.1%	566	73.6%	1,085	53.9%
Urban/rural	Rural	3	1.3%	76	3.5%	0	0	5	0.7%	148	7.3%
	Urban	222	98.7%	2,116	96.5%	231	100%	764	99.3%	1,866	92.7%

Note: All values are presented as number and percentages unless otherwise designated.
Abbreviations: AML, acute myeloid leukemia; GVHD, graft-vs-host disease; HSCT, hematopoietic stem-cell transplantation; MDS, myelodysplastic syndrome; SNF, skilled nursing facility.