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ORIGINAL RESEARCH

Use of Antifungals and Outcomes Among Inpatients at Risk of Invasive Aspergillosis or Mucormycosis in the USA: A Retrospective Cohort Study

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ABSTRACT

Introduction: Prophylaxis and treatment of invasive aspergillosis (IA) and mucormycosis (IM) within a real-world US inpatient setting is undocumented since the introduction of isavuconazole. This retrospective medical record review aimed to describe characteristics, triazole use, and outcomes among inpatients across the USA who initiated antifungal monotherapy (AFMT) as prophylaxis or treatment of IA/IM.

Methods: A convenience sample of US physicians abstracted data from randomly selected records of hospitalized patients aged ≥ 18 years initiating AFMT (amphotericin B, isavuconazole, voriconazole, or posaconazole) as prophylaxis or treatment of IA/IM between 2013 and 2017. Retrieved data included background characteristics, dosage and duration of AFMT, healthcare resource use, and survival. Characteristics and outcomes were compared (prophylaxis vs treatment) using Fisher's exact and one-way analysis of variance tests where applicable. Exploratory Kaplan–Meier analyses described overall and inpatient survival.

Results: Physicians ($n = 23$) retrieved 124 patient records (43 prophylaxis; 81 treatment). Median duration of first-line AFMT was 14 days (range 1–603 days) and 19 days (range 3–351 days) in the prophylaxis and treatment groups, respectively. One patient received second-line therapy. Median duration of hospitalization was 29 days (range 4–259 days) and 31 days (range 6–980 days) in the prophylaxis and treatment groups, respectively. Admission to intensive care occurred in 14% and 52% of patients in the prophylaxis and treatment groups, respectively. At the time of data retrieval, overall and inpatient survival rates in the prophylaxis group were 88% and 87%, respectively, and in the treatment group were 66% and 76%, respectively.

Conclusions: This study documented real-world prophylactic and therapeutic AFMT use for IA/IM and associated outcomes among hospitalized patients in the USA since approval of isavuconazole. IA/IM were associated with lengthy hospital stays commonly requiring intensive care. Prophylactic and therapeutic AFMT dosages and duration generally followed recommendations and switching between agents was rare.

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INTRODUCTION

Invasive fungal infections (IFIs) such as invasive aspergillosis (IA) and mucormycosis (IM) can result in severe disease and are potentially fatal [1–5]. An increase in the number of deaths from IFIs has been documented [6–9], and rates of IA- and IM-related hospitalizations have increased since 2000 [10]. As the number of patients treated with immunosuppressive therapy and intensive chemotherapy regimens grows, the incidence of these infections has increased [2].

Despite treatment advancements and clinical guidelines, the prevention, diagnosis, and treatment of IFIs remain challenging. Randomized clinical trials have investigated the efficacy of mold-active triazoles [11–13], but are limited in the depth of information they can provide due to the rarity of the conditions, the challenges of recruiting severely ill and immunocompromised patients, and the heterogeneity of the underlying disease. Observational cohort studies provide opportunities to examine real-world current approaches to the diagnosis and management of IFIs, and offer a greater ability to examine the breadth of both the underlying heterogeneity and the severity of the disease [14–17]. The results of such studies have broadened our understanding of unmet treatment needs and have informed the development of current guidelines [18]. However, no real-world evidence of prevention and treatment strategies within this patient population has been published since the introduction of isavuconazole in the USA in 2015.

The study presented herein examines real-world prevention and treatment strategies for IA/IM in the inpatient setting in the USA since 2013. Specifically, this study aimed to describe the characteristics of hospitalized patients across the USA who initiated prophylaxis or treatment with mold-active triazoles or amphotericin B for IA or IM; document dosage and duration of mold-active triazole use; and evaluate patient outcomes pertinent to healthcare resource use and survival.

METHODS

Study Design and Population

A retrospective cohort study of patient medical records from hospitals across the USA was conducted. Records were eligible if patients were aged 18 years or older at the time of hospitalization and had initiated antifungal monotherapy (AFMT) during the hospitalization for either prophylaxis or treatment of IA or IM between January 1, 2013 and August 31, 2017. The antifungal agents evaluated were prespecified and based on current clinical guidelines [18]: amphotericin B (any formulation), isavuconazole, voriconazole, and posaconazole. No restrictions were placed on the use of antifungals following initiation of these agents. Eligible physicians were hospital-based and currently managing patients with IFIs, had treated at least one patient for IA/IM per year, had acted as a key decision-maker in the management of IA/IM, and were experienced with the antifungal agents of interest.

Data Retrieval Methods

Data were retrieved between January 26, 2018 and March 9, 2018, inclusive. Data from hospitalization until the last medical record entry or documented date of death were entered by physicians into an anonymized, web-based electronic data retrieval form developed by the study authors (KS, VPP). During development, the data retrieval form was reviewed and tested by two eligible physicians within the USA to assess its functionality and availability of the requested data elements.

A convenience sampling approach was used to recruit physicians, and no quotas were applied [19]. A quasi-random method was applied for patient selection by asking physicians to select four records for patients whose last name began with a randomly generated letter (A through Z, inclusive). If no eligible

patient record was identified, the physician was asked to select a patient whose last name began with the next letter in alphabetical order. Physicians continued this process until 4 patients per institution had been identified (one for each of amphotericin B, isavuconazole, voriconazole, and posaconazole).

The data retrieved consisted of: sociodemographic/clinical characteristics at the time of hospitalization; dates of hospitalization and antifungal therapy initiation; antifungal drugs used, including reason for initiation; therapy start/stop dates, dose, and frequency; changes in therapy regimens and attributed reasons for change, if any; hospital discharge date; admission to an intensive care unit (ICU); need for mechanical ventilation; hospital readmission within 30 days of discharge; vital status at the time of data abstraction (i.e., dead or alive); date of death; and date of last medical record entry.

All procedures performed in studies involving human participants were in accordance with the ethical standards of RTI International's institutional review board (Research Triangle Park, North Carolina) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was not sought due to the nature of the study: all retrieved data were anonymous and were those collected as part of routine diagnosis and treatment. There was no effect of the review on patient care. Physicians abstracting the data were treating physicians who had legitimate access to the medical records. RTI International's institutional review board determined that this study met all criteria for exemption from ethical considerations.

Statistical Analysis

Patient characteristics are described by reason for initiation of AFMT (i.e., prophylaxis or treatment). Outcomes data are described by reason for initiation of AFMT and by antifungal agent used.

Patient characteristics are reported as frequencies and percentages for categorical variables based on the number of patients with no missing data for each variable. Means, standard deviations (SDs), medians, and ranges are reported for continuous variables.

The retrieved data were used to calculate duration of hospitalization, duration of antifungal therapy, time to admission to ICU, time to hospital readmission within 30 days of discharge, rate of overall survival, and rate of inpatient survival. The date of the last medical record entry was used in calculations if patients were still receiving the AFMT of interest at the time of data retrieval. If patients died during the hospitalization or after discharge, the date of death was used to calculate durations. For overall survival, patients still alive at the time of data retrieval were censored at the date of the last available medical record entry. For inpatient survival, patients still alive and hospitalized at the time of data retrieval were censored at the date of the last available medical record entry, and discharged patients were censored at the date of discharge from hospital. Patients with undocumented status were excluded from the calculation of outpatient survival rates, and patients with an undocumented hospital discharge status were excluded from the calculation of inpatient survival rates.

Patient characteristics and outcomes were compared using Fisher's exact and one-way analysis of variance tests where applicable; P values are reported, with $P \leq 0.05$ suggestive of statistically significant differences between patients initiating AFMT as prophylaxis or treatment. Exploratory Kaplan–Meier analyses were performed to describe overall and inpatient survival.

RESULTS

Physician Characteristics

Twenty-three physicians from 23 sites participated and abstracted data from 124 patient medical records ($n = 31$ for each antifungal agent). Eight physicians abstracted data for 2 patients per antifungal agent (i.e., 8 records); 15 physicians abstracted data for one patient per antifungal agent (i.e., 4 records). Sixteen physicians abstracted data related to prophylaxis; 21 physicians abstracted data related to

treatment. Geographically, 25% of the physicians who abstracted data related to prophylaxis operated in the Midwest, 38% in the Northeast, 19% in the West, and 19% in the South of the USA. Of the physicians who abstracted data related to treatment, 29% operated in the Midwest, 24% in the Northeast, 29% in the West, and 19% in the South. Most physicians reported practicing in community (prophylaxis: 38%; treatment: 52%), academic/teaching (prophylaxis: 25%; treatment: 24%), or public (prophylaxis: 25%; treatment: 19%) hospitals. The most common medical specialties were infectious diseases (prophylaxis: 25%; treatment: 38%), oncology (prophylaxis: 38%; treatment: 29%), and intensive care (prophylaxis: 19%; treatment: 19%).

Patient Characteristics at Hospital Admission

A total of 43 records were abstracted related to patients receiving AFMT as prophylaxis; a total of 81 related to patients receiving AFMT as treatment. Table 1 documents the demographic and background clinical characteristics of the sample, by reason for AFMT initiation (i.e., prophylaxis or treatment).

There were no significant differences in demographic characteristics between patients who initiated AFMT as prophylaxis versus treatment (Table 1). Mean age (± SD) was 53.4 (± 14.6) and 51.3 (± 16.0) years for patients receiving prophylaxis and treatment, respectively. Most patients were male (prophylaxis: 63%; treatment: 64%), overweight (mean body mass index, kg/m^2 [± SD]: prophylaxis: 26.6 [± 3.3]; treatment: 25.9 [± 3.6]), and white (prophylaxis: 65%; treatment: 58%).

IFIs occurred most commonly in the lung, blood, or sinuses; patients initiating AFMT as treatment were significantly more likely than those initiating AFMT as prophylaxis to have an IFI manifesting in the lung (63% vs 35%; $P < 0.01$) or blood (42% vs 16%; $P < 0.01$) (Table 1). No significant differences in underlying diseases or host risk factors were observed based on the reason for AFMT initiation. The most frequent underlying diseases were acute myeloid leukemia and hematopoietic stem cell transplantation. Host risk factors most commonly noted in both the prophylaxis and treatment groups were prolonged neutropenia and fungal or bacterial infection. Less than 20% of the sample had received antifungal therapy at any time prior to their hospitalization.

Patients receiving AFMT as prophylaxis were significantly more likely to be receiving posaconazole than those receiving AFMT as treatment (37% vs 19%; $P < 0.05$) (Table 1). No significant differences were observed between the prophylaxis and treatment groups with respect to receipt of amphotericin B, isavuconazole, or voriconazole.

Antifungal Therapy

Reason for AFMT Initiation

Among patients initiating AFMT as treatment, most had proven infections (57%) as defined by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group definitions [20]. The majority of infections (63%) were proven via histopathologic, cytopathologic, or direct microscopic examination.

A total of 56 patients received AFMT as treatment for IA (45.2%); 10 patients received AFMT as treatment for IM (8.1%); 5 patients received AFMT as treatment for both IA and IM (4.0%); and 1 patient received AFMT as treatment for other IFI (0.8%). A total of 17 patients received AFMT as prophylaxis for IA (13.7%); 8 patients received AFMT as prophylaxis for IM (6.5%); 10 patients received AFMT as prophylaxis for both IA and IM (8.1%); and 8 patients received AFMT as prophylaxis for other IFI (6.5%).

Duration and Dosage of First-line AFMT

Median duration of first-line AFMT was 14 days (range 1–603 days) for patients initiating AFMT as prophylaxis, and 19 days (range 3–351 days) for patients initiating AFMT as treatment (mean [± SD] 60.0 [± 118.0] vs 40.5 [± 58.8]; $P = 0.16$) (Fig. 1).

Table 1 Patient characteristics at hospitalization

Characteristic	Prophylaxis $n = 43$	Treatment $n = 81$	P value[a]
Sex, *n* (%)			
Male	27 (62.8)	52 (64.2)	> 0.999
Female	16 (37.2)	29 (35.8)	
Age, years			
Mean (SD)	53.4 (14.6)	51.3 (16.0)	0.365
Median	54.2	51.6	
Min–max	23–77	21–86	
Race, *n* (%)			
White	28 (65.1)	47 (58.0)	0.782
Black or African American	10 (23.3)	15 (18.5)	
Asian	5 (11.6)	15 (18.5)	
American Indian or Alaska Native	0 (0.0)	1 (1.2)	
Other	0 (0.0)	1 (1.2)	
No answer	0 (0.0)	2 (2.5)	
BMI, kg/m^2			
Mean (SD)	26.6 (3.3)	25.9 (3.6)	0.201
Median	25.8	25.5	
Min–max	21.3–35.4	21.0–40.4	
Location of fungal infection manifestation (occurring in > 10% total population), *n* (%)[b]			
Lung	15 (34.9)	51 (63.0)	0.004
Blood	7 (16.3)	34 (42.0)	0.005
Sinus	9 (20.9)	18 (22.2)	> 0.999
Skin	5 (11.6)	9 (11.1)	> 0.999
Primary underlying condition (occurring in > 10% total population), *n* (%)			
Acute myeloid leukemia	8 (18.6)	12 (14.8)	0.614
Hematopoietic stem cell transplantation	8 (18.6)	10 (12.3)	0.424
Diabetes or uncontrolled hyperglycemia	6 (14.0)	10 (12.3)	0.785
Solid-organ transplant	5 (11.6)	10 (12.3)	> 0.999

Table 1 continued

Characteristic	Prophylaxis *n* = 43	Treatment *n* = 81	*P* value[a]
Risk factors (occurring in > 10% total population), *n* (%)[b]			
Prolonged neutropenia	11 (25.6)	32 (39.5)	0.165
Fungal or bacterial infection	9 (20.9)	26 (32.1)	0.214
Allogeneic stem cell transplantation	8 (18.6)	12 (14.8)	0.614
Prolonged or high-dose use of corticosteroids	5 (11.6)	12 (14.8)	0.786
Other form of infection	7 (16.3)	8 (9.9)	0.386
No risk factors reported	5 (11.6)	10 (12.3)	> 0.999
Comorbid conditions (occurring in > 10% total population), *n* (%)[b]			
Hematological malignancy	19 (44.2)	27 (33.3)	0.248
Diabetes[c]	7 (16.3)	18 (22.2)	0.489
Mild hepatic disease[d]	3 (7.0)	16 (19.8)	0.070
Moderate pulmonary disease[e]	5 (11.6)	14 (17.3)	0.448
Moderate to severe renal impairment[f]	5 (11.6)	10 (12.3)	> 0.999
QTc prolongation, *n* (%)			
No	38 (88.4)	72 (88.9)	> 0.999
Unknown	5 (11.6)	9 (11.1)	
Prior antifungal therapy at any time, *n* (%)			
Yes	8 (18.6)	14 (17.3)	0.853
No	29 (67.4)	52 (64.2)	
Unknown	6 (14.0)	15 (18.5)	
Antifungal agent received, *n* (%)			
Amphotericin B	7 (16.3)	24 (29.6)	0.129
Isavuconazole	9 (20.9)	22 (27.2)	0.518
Voriconazole	11 (25.6)	20 (24.7)	> 0.999
Posaconazole	16 (37.2)	15 (18.5)	0.030

BMI body mass index, *max* maximum, *min* minimum, *SD* standard deviation

[a] Differences were assessed using the Kruskal–Wallis test for continuous variables and Fisher's exact test for categorical variables

[b] Multiple responses allowed

[c] Requiring insulin or oral hypoglycemics

[d] Chronic hepatitis, bilirubin > upper limit of normal (ULN) to 1.5 × ULN, or aspartate aminotransferase/alanine aminotransferase > ULN to 2.5 × ULN

[e] The diffusing capacity for carbon monoxide (DLCO) and/or forced expiratory volume in 1 s (FEV_1) 66–80% or dyspnea on slight activity

[f] Creatinine clearance < 50 mL/min

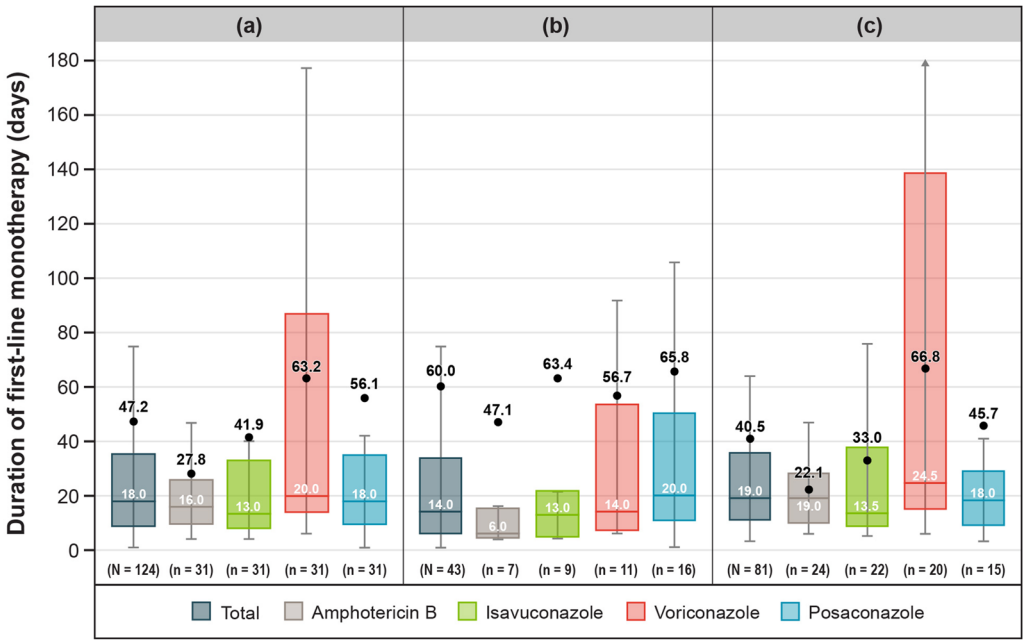

Fig. 1 Duration of antifungal monotherapy (AFMT). **a** Overall duration of first-line AFMT, total study population. **b** Duration of prophylaxis with first-line AFMT, prophylaxis group. **c** Duration of treatment with first-line AFMT, treatment group. Whiskers represent the minimum and maximum values excluding outliers; horizontal line represents the median; the upper and lower portions of the box represent the upper and lower quartiles; the circle represents the mean. Median daily dosage for prophylaxis: amphotericin B, 2.4 mg/kg (range 1.0–7.4 mg/kg); isavuconazole, 372 mg (range 20–1116 mg); voriconazole, 240 mg (range 5–800 mg); posaconazole, 300 mg (range 15–600 mg). Median daily dosage for treatment: amphotericin B, 2.3 mg/kg (range 0.2–6.7 mg/kg); isavuconazole, 372 mg (range 10–1116 mg); voriconazole, 400 mg (range 100–650 mg); posaconazole, 300 mg (range 25–400 mg)

In the prophylaxis group, 7 patients received first-line amphotericin B for a median duration of 6 days (range 4–280 days) (Fig. 1b). The median daily dosage was 2.4 mg/kg (range 1.0–7.4 mg/kg) (recommended dose: 3–6 mg/kg/day liquid formulation [18]). Nine patients received isavuconazole as prophylaxis for a median duration of 13 days (range 4–291 days) at a median daily dose of 372 mg (range 20–1116 mg) (recommended dose: 372 mg/day, after a 2-day loading regimen [18]). Eleven patients received voriconazole as prophylaxis for a median duration of 14 days (range 6–351 days) at a median daily dose of 240 mg (range 5–800 mg) (recommended dose: 400 mg/day [18]). Sixteen patients received posaconazole as prophylaxis for a median duration of 20 days (range 1–603 days) at a median daily dose of 300 mg (range 15–600 mg) (recommended dose: 300 mg/day [18]).

In the treatment group, 24 patients received first-line amphotericin B for a median duration of 19 days (range 6–64 days) (Fig. 1c). The median daily dosage was 2.3 mg/kg (range 0.2–6.7 mg/kg). Twenty-two patients received isavuconazole as treatment for a median duration of 14 days (range 5–165 days) at a median daily dose of 372 mg (range 10–1116 mg). Twenty patients received voriconazole as treatment for a median duration of 25 days (range 6–217 days) at a median daily dose of 400 mg (range 100–650 mg). Fifteen patients received posaconazole as treatment for a median duration of 18 days (range 3–351 days) at a median daily dose of 300 mg (range 25–400 mg).

Changes in Treatment or Prophylaxis Following Initiation

Seven treatment changes were documented (Table 2). Two dose reductions were observed:

one for a patient receiving amphotericin B due to nephrotoxicity and one for a patient receiving voriconazole for undocumented reasons. One dose increase due to lack of efficacy occurred in a patient receiving posaconazole. One treatment switch from isavuconazole to voriconazole occurred due to elevated liver enzymes. Treatment was discontinued in 3 patients due to lack of efficacy (amphotericin B) or for undocumented reasons (isavuconazole and voriconazole).

Healthcare Resource Use

Duration of Initial Hospitalization

Of the 43 records extracted related to prophylaxis, physicians provided complete hospitalization date information for 24 patients (56%); of the 81 records related to treatment, physicians provided complete hospitalization date information for 65 patients (80%) (Fig. 2a). Median duration of hospitalization was 29 days (range 4–259 days) in the prophylaxis group versus 31 days (range 6–980 days) in the treatment group (mean [± SD] = 37.8 [± 50.7] vs 84.6 [± 188.1]; $P = 0.09$). Patients initiated AFMT shortly after hospitalization. Median duration of hospitalization following AFMT initiation was 25 days (range 4–259 days) in the prophylaxis group versus 28 days (range 5–968 days) in the treatment group (mean [± SD] = 32.9 [± 51.2] vs 79.1 [± 187.1]; $P = 0.07$).

Among patients receiving prophylaxis, those initiating therapy with posaconazole or voriconazole were hospitalized for a median duration of 30 days (range 5–259 days) or 28 days (range 11–29 days), respectively, compared with 20 days (range 4–41 days) for amphotericin B and 10 days (range 4–35 days) for isavuconazole (Fig. 2b).

Among patients receiving treatment, those initiating therapy with voriconazole were hospitalized for a median of 42 days (range 6–135 days), compared with 32 days (range 7–147 days) for amphotericin B, 31 days (range 8–980 days) for posaconazole and 21 days (range 8–189 days) for isavuconazole (Fig. 2c).

Table 2 Changes in treatment or prophylaxis following initiation

	Amphotericin B ***n*** **= 31** ***n*** **(%)**	**Isavuconazole** ***n*** **= 31** ***n*** **(%)**	**Voriconazole** ***n*** **= 31** ***n*** **(%)**	**Posaconazole** ***n*** **= 31** ***n*** **(%)**
Dose reduction	1 (3.2)	0 (0.0)	1 (3.2)	0 (0.0)
	Due to nephrotoxicity		Rationale undocumented	
Dose increase	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)
				Due to lack of efficacy
Treatment switch	0 (0.0)	1 (3.2)	0 (0.0)	0 (0.0)
		Due to elevated liver enzymes		
Discontinuation	1 (3.2)	1 (3.2)	1 (3.2)	0 (0.0)
	Due to lack of efficacy	Rationale undocumented	Rationale undocumented	
None	25 (80.6)	26 (83.9)	28 (90.3)	29 (93.5)
Unknown	4 (12.9)	3 (9.7)	1 (3.2)	1 (3.2)

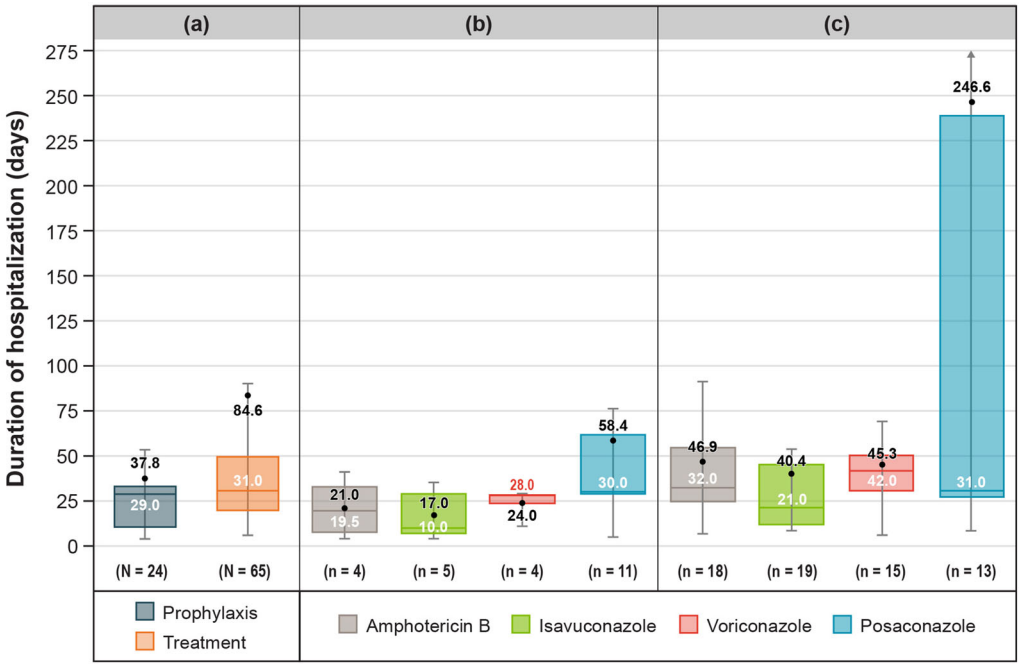

Fig. 2 Duration of initial hospitalization. **a** Overall duration of initial hospitalization, total study population. **b** Duration of initial hospitalization for patients receiving first-line AFMT as prophylaxis. **c** Duration of initial hospitalization for patients receiving first-line AFMT as treatment. Whiskers represent the minimum and maximum values excluding outliers; horizontal line represents the median; the upper and lower portions of the box represent the upper and lower quartiles; the circle represents the mean. Of the 124 patient records extracted, physicians provided complete and usable hospitalization date information for 89 patients. AFMT, antifungal monotherapy

Emergent Care During the Initial Hospitalization

Mechanical ventilation was required by 5% of patients on prophylaxis and 31% of patients on treatment ($P = 0.001$). Mechanical ventilation use in patients receiving treatment was most common among patients receiving voriconazole (45% vs 40% for posaconazole, 32% for isavuconazole, and 13% for amphotericin B). Admission to the ICU occurred in 14% of patients on prophylaxis and 52% of patients on treatment ($P < 0.001$). ICU admission rates for patients receiving treatment were similar regardless of antifungal agent used (55% for isavuconazole, 55% for voriconazole, 53% for posaconazole, and 46% for amphotericin B).

Hospital Readmission Following Discharge

Of the 106 patients who did not die during the initial hospitalization, 98 (92%) had been discharged by the time of data retrieval. Physicians were aware of the readmission status of 63 of these discharged patients. One patient was readmitted within 30 days of discharge due to continued antifungal infection; this patient received isavuconazole as treatment during their initial hospitalization.

Survival

At the time of data retrieval, 31 patients (25%) were known to have died (5 prophylaxis; 26 treatment). Overall survival rates were 88% (36/41) in the prophylaxis group and 66% (50/76) in the treatment group. Of the 31 deaths, 16 were reported to be caused by or related to IA or IM. Among patients receiving AFMT as prophylaxis, those who died were receiving either amphotericin B (2 patients), isavuconazole (1 patient), or voriconazole (2 patients). Among patients

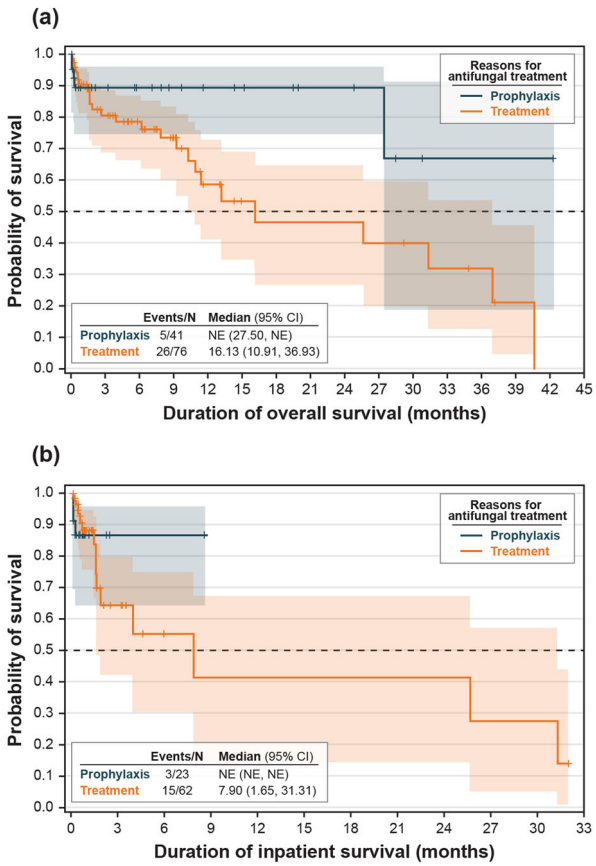

Fig. 3 Survival. **a** Overall survival by reason for AFMT initiation. **b** Inpatient survival by reason for AFMT initiation. Tick marks represent censoring; shaded areas represent the 95% confidence intervals. CI, confidence interval; NE, not established

receiving AFMT as treatment, deaths occurred more commonly among patients receiving voriconazole or posaconazole (9 and 8 patients, respectively) than among patients receiving isavuconazole or amphotericin B (6 and 3 patients, respectively). For patients with a known vital status and complete date information ($n = 117$), the median overall survival duration was not estimable for patients receiving prophylaxis and was 16.1 months (95% confidence interval [CI], 10.9, 36.9) for patients receiving treatment (Fig. 3a).

Eighteen of the 124 patients included in the study (15%) were known to have died during hospitalization (3 prophylaxis; 15 treatment). At the time of data retrieval, inpatient survival rates were 87% (20/23) in the prophylaxis group and 76% (47/62) in the treatment group. For patients with a known vital status and complete date information ($n = 85$), the median duration of inpatient survival was not estimable for patients receiving prophylaxis and was 7.9 months (95% CI, 1.7, 31.3) for patients receiving AFMT as treatment (Fig. 3b).

DISCUSSION

This retrospective cohort study has described the characteristics of adult inpatients with, or at risk of, IA or IM who initiated AFMT with amphotericin B, isavuconazole, voriconazole, or posaconazole during their hospital stay. It is one of few studies to provide real-world data on the profile of such patients [14, 16, 17, 21] and is the first to document clinical practice and outcomes in a diverse population since the US introduction of isavuconazole. Our findings demonstrated that: IA/IM were associated with lengthy hospital stays commonly requiring ICU admission; prophylactic and therapeutic dosages and duration of AFMT generally followed published clinical guidelines [18]; and hospital readmission and switching between agents occurred rarely.

The demographic and clinical profiles of the study population were similar to those reported previously [22, 23]. Most of the population were white males who were overweight, with fungal infections most commonly manifesting in the lungs, blood, and sinuses, and the coexistence of many comorbidities [24, 25]. The high level of heterogeneity in underlying diseases known to be associated with IA and IM was evident, with no one condition accounting for more than 20% of the sample.

The 2016 Infectious Diseases Society of America guidelines for the management of IA recommend triazoles as the preferred agents for treatment and prevention [18]. In our sample, amphotericin B, isavuconazole, and voriconazole were most commonly associated with treatment, while posaconazole was most commonly associated with prophylaxis.

Real-world data on the duration of antifungal prophylaxis and treatment in the inpatient

setting are lacking. When used as treatment, the guidelines recommend that therapy be continued for a minimum of 6–12 weeks. In our study, therapy for treatment was received, on average, for just under 6 weeks. However, the data were skewed, with only 12 of the 81 patients receiving treatment for longer than 7.5 weeks, and thus the median treatment duration was just under 3 weeks. Most of the study population had been discharged by the start of our data retrieval period, with only one patient reported to have been readmitted to hospital within 30 days of discharge. Deaths related to IA and IM were uncommon.

Given the lack of real-world evidence about the duration of antifungal prophylaxis and treatment in the inpatient setting, further research is warranted to examine the extent to which the durations and outcomes identified are representative of common practice. Such information may be beneficial for the further development of treatment guidelines in the USA.

Our study revealed wide variation in AFMT dosages, particularly for isavuconazole (median dosage [range]: prophylaxis, 372 [20–1116] mg/day; treatment, 372 [10–1116] mg/day). This is interesting in light of a recently reported real-world case of a 23-year-old male with severe aplastic anemia in whom IA was successfully controlled through use of low-dose isavuconazole [26]. Blood concentrations of isavuconazole remained high after reducing the dose from 200 mg/day to 100 mg/day in response to increased liver function tests. This high concentration may be related to the patient taking cyclosporine, which has been shown to increase peak concentration of isavuconazole by 30% via inhibition of CYP3A4 [27].

Treatment switching in the inpatient setting has been studied in follow-on clinical trial settings [28] and in retrospective observational settings in which eligibility criteria involved patients who switched treatment [15], but little is known about the occurrence of and reasons for real-world treatment switching. Our results indicate that switching agents is rare among hospitalized patients in the USA with, or at risk of, IA or IM. Current treatment guidelines recommend salvage therapy with a different class of antifungal, tapering or reversal of underlying immunosuppression, and surgical removal of necrotic lesions [18]. Our study did not assess treatment of the underlying condition, so the extent to which non-antifungal treatment was tapered or reversed is unknown.

The overall mortality rate we identified in the treatment group (32% [26/81] at the time of data retrieval) was similar to previously reported data from real-world settings [29–31]). However, our study reported a low in-hospital mortality rate (19% [15/81]) in the treatment group compared with previously reported mortality rates for ICU patients with IA (46–80%) [25]. In our sample, 52% of the treatment group were admitted to the ICU, suggesting that the group as a whole were less sick than the patients in these previous reports. The low in-hospital mortality rate in the treatment group may also be explained in part by the fact that previous studies predate the availability of improved diagnostics, treatment guidelines, and the newer antifungal agents studied here. The diversity of our population in terms of underlying disease and the respective small sample sizes may also have contributed to the low inpatient mortality rate observed. In addition, the estimated survival results we have presented should be interpreted with caution because most of the censoring occurred in the first 12 months [32]. Moreover, no adjustments were made, and patients who were prescribed isavuconazole had a shorter opportunity for follow up compared with patients who were prescribed the other antifungal agents (i.e., the earliest available entry date for this study was 2013, but isavuconazole was not approved in the USA until 2015).

Retrospective medical record review studies are subject to limitations. The patients selected for study inclusion represented a convenience sample and therefore the findings may have limited generalizability. Data were limited to information available in the records, and information on services received outside the physician's care setting not recorded in the record were unavailable. Additionally, some data were missing, particularly date information. Although data checks were in place to assess the internal consistency of the entered

data, an independent reviewer did not validate the responses; reliability was therefore not assessed. Further, the study did not assess the severity of patients' underlying conditions. It is plausible that some of the observed differences between the antifungal agents may reflect condition severity rather than prophylactic or therapeutic efficacy. In addition, this study involved small numbers of patients per antifungal agent, and the groups were non-contemporaneous; other host- and infection-related issues may therefore have influenced resource utilization and survival outcomes.

This study aimed to document patient profiles and treatment patterns associated with the use of each AFMT, and the associated healthcare resource utilization and survival outcomes. To allow the patterns and outcomes for each therapy to be examined, considering the rarity of the condition, we imposed selection criteria to ensure an equal number of patients received each AFMT. However, this approach does not reflect real-world use of AFMT, and our findings do not reflect the frequency with which each AFMT is used in the inpatient setting. Moreover, participating physicians must have prescribed each AFMT: physicians who prescribe a particular AFMT only were not included. It is plausible that different hospitals across the USA have different prescribing practices, for example, due to AFMT familiarity and access. Therefore, the study results cannot be used to inform understanding of the distribution of use of each AFMT across the USA.

Our study has focused on patients with, or at risk of, IA or IM who received AFMT. However, combination therapy is now used increasingly to treat IFIs in attempts to improve outcomes, particularly for more severe cases. A randomized controlled trial in patients with hematological malignancies or hematopoietic cell transplantation has reported that treatment of IA with voriconazole plus anidulafungin was associated with a statistically nonsignificant but clinically meaningful survival benefit compared with voriconazole alone [33]. A recent small retrospective chart review of medical records has reported a significantly lower mortality rate in patients with non-*Aspergillus* IFIs, including mucormycosis, treated with combination antifungal therapy compared with AFMT [34]. If, indeed, severe IA/IM cases tend to receive combination antifungal therapy, the methods employed in our study may have introduced a bias by selecting less severe cases receiving AFMT and patients receiving AFMT as prophylaxis. This study is the first to document real-world, inpatient, prophylactic and therapeutic use of antifungal agents for IFIs and the associated outcomes since isavuconazole was approved in the USA. The findings provide valuable evidence of contemporary practices that warrant further investigation using alternative data sources such as patient registries. Research already underway aims to build upon the current findings by extending study to the outpatient setting and by replicating our approach in a large registry of patients treated with systemic mold-active triazoles in the USA (ClinicalTrials.gov identifier: NCT03066011).

CONCLUSIONS

This retrospective medical record review has described the characteristics of a sample of hospitalized patients with, or at risk of, IA or IM in the USA. In addition, the real-world use of mold-active triazoles for prevention and treatment of IA/IM, as well as associated outcomes, were documented. IA and IM most commonly manifested in the lungs, blood, and sinuses, and were associated with lengthy hospital stays that frequently required ICU admission. Real-world prophylaxis and treatment generally followed published clinical guidelines. Subsequent hospital readmission and switching between agents were rare. These findings highlight the importance of IFI monitoring during hospitalization and the use of appropriate prophylaxis and treatment.

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Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of RTI International's institutional review board (Research Triangle Park, North Carolina) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was not sought due to the nature of the study: all retrieved data were anonymous and were those collected as part of routine diagnosis and treatment. There was no effect of the review on patient care. Physicians abstracting the data were treating physicians who had legitimate access to the medical records. RTI International's institutional review board determined that this study met all criteria for exemption from ethical considerations.

Data Availability. Access to anonymized individual participant level data will not be provided for this study as it meets one or more of the exceptions described on http://www.clinicalstudydatarequest.com under "Sponsor Specific Details for Astellas".

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