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Opportunities for Antimicrobial Stewardship Among Pediatric Patients Prescribed Combination Antifungal Therapy

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OBJECTIVE Combination antifungal therapy (CAF) may be prescribed to treat invasive fungal infections (IFIs). Data on the incidence of CAF among the pediatric population are limited. Antimicrobial stewardship for CAF includes therapeutic drug monitoring (TDM) and monitoring for adverse events. Primary outcome was to determine the incidence of CAF prescribed for documented proven, probable, and possible IFI. Secondary outcomes were to determine initial dose of antifungal therapy, determine incidence of adverse events, and evaluate our practice of TDM.

METHODS Medical charts of patients who received CAF for proven, probable, or possible IFI within 6 years were reviewed. Patients age ≤18 years, prescribed CAF (defined as a second antifungal therapy started ≤72 hours of initial antifungal therapy) for at least 72 hours, and with normal liver function test results were included.

RESULTS 57 patients received CAF for 72 separate episodes: 35 episodes were proven IFI, 11 were probable IFI, and 26 were possible IFI. Initial dose of antifungal therapy varied, and 29.1% received a loading dose. A total of 10 patients experienced 14 adverse events that were related to antifungal therapy. In 63.8% of CAF episodes, TDM was conducted. Target antifungal concentrations were documented for 10 CAF episodes. Reason for discontinued of CAF was documented for 35 episodes. Of these episodes, 74% were discontinued after therapeutic antifungal concentrations were achieved.

CONCLUSIONS There are opportunities for antimicrobial stewardship interventions in the method of TDM and monitoring for adverse events that could aid in management of CAF.

ABBREVIATIONS CAF, combination antifungal therapy; FDA, US Food and Drug Administration; IA, invasive aspergillosis; IDSA, Infectious Diseases Society of America; IFI, invasive fungal infections; TDM, therapeutic drug monitoring

KEYWORDS antimicrobial stewardship; invasive fungal infections

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Introduction

Invasive fungal disease is a significant cause of morbidity and mortality among immunocompromised and hospitalized pediatric patients.[1,2] Combination antifungal therapy (CAF) is recommended by Infectious Diseases Society of America (IDSA) guidelines for certain diagnoses of *Cryptococcus*, candidal infections, and invasive aspergillosis.[3-5] With the addition of newer antifungal agents, treatment options have expanded, including opportunities for CAF. The purpose of prescribing empiric CAF may be due to the complexity of diagnosis, high mortality rates associated with fungal disease, maximizing timely achievement of therapeutic drug concentrations, increasing spectrum of therapy, and targeting multiple targets or metabolic pathways for additive or synergistic effects.[4,6,7] Potential advantages of prescribing CAF include enhanced rate and extent of killing (additivity or synergy), increased spectrum of activity, and decreased likelihood of resistance.[8] Postulated disadvantages of CAF include decreased rate and extent of killing (antagonism), increased risk of drug interactions, toxicity, cost, lack of standard methods to conduct *in vitro* synergy testing, and uncertainty as to how to interpret findings.[4,8,9]

Our study investigated the incidence of CAF for documented proven, probable, and possible invasive fungal infection (IFI) within a pediatric hospital. In addition, we observed the dose of antifungal therapy prescribed, incidence of adverse events, and therapeutic drug monitoring (TDM) among patients prescribed combination therapy.

Table 1. Patient and Disease State Characteristics

Demographics	Results
Total episodes	72
Unique patients, n	57
Age at admission, median (IQR), yr	10 (6–13)
Sex, male, n (%)	32 (56)*
Weight, median (IQR), kg	32.2 (18.05–51.4)
Race, white, n (%)	47 (82.4)*
Previous history of antifungal therapy for suspected, proven, possible, or probable IFI, n (%)	26 (45.6)*
Underlying malignancy, n (%)*	
Acute lymphoblastic leukemia	20 (35)
Acute myeloid leukemia	11 (19.2)
Lymphoma	12 (21)
Aplastic anemia	5 (8.7)
Solid tumor	5 (8.7)
Solid-organ transplant recipient	4 (7)
Underwent stem cell transplantation prior to IFI, n (%)	12 (15.8)
Time between hematologic/oncologic diagnosis or stem cell transplantation and presentation with IFI, median (range), days	68 (1–3285); average = 225 days
Status of underlying disease at time of diagnosis of IFI, n (%)*†	
Remission	36 (54.3)
Active	36 (52.6)

IFI, invasive fungal infections

* Percentage of unique patients.

† There were 4 unique patients who had multiple combination antifungal therapy episodes who received a diagnosis of either active or remission of underlying disease.

Methods

Our retrospective study was conducted at a freestanding tertiary care pediatric hospital. Our institution has 302 beds, with approximately 12,000 admissions, 57,000 emergency department visits, and 18,000 surgeries a year. Our hospital has pediatric, cardiac, and neonatal intensive care units, and offers stem cell transplantation, solid organ transplantation, and fetal surgery. Primary outcome of this study was to determine the incidence of CAF prescribed for documented proven, probable, and possible IFI. Secondary outcomes were to 1) determine the initial dose of antifungal therapy prescribed, 2) determine the incidence of adverse events, and 3) evaluate TDM among patients prescribed CAF for IFI.

Medical charts of patients who received CAF for proven, probable, or possible IFI (as per European Organization for the Research and Treatment of Cancer criteria)[7] from January 1, 2013, through December 31, 2018, were reviewed. Patients were included if they were age 18 years or younger at the time that CAF was initiated and had received CAF (defined as a second antifungal therapy started ≤72 hours of initial antifungal therapy) for at least 72 hours for proven, probable, or possible IFI. Exclusion criteria included abnormal liver function testing (defined as alanine aminotransferase or aspartate aminotransferase >10 times the upper limit of normal, total bilirubin >5 times the upper limit of normal, or alkaline phosphatase >5 times the upper limit of normal) at baseline or if combination therapy was administered for less than or equal to 72 hours. As a secondary outcome involved evaluation of the incidence of hepatic injury, we excluded patients with preexisting abnormal liver chemistries. Patients could be included for multiple occurrences in which CAF was administered or if there was a change in one of the antifungal agents prescribed for CAF. Each occurrence of CAF was referred to as an episode of CAF.

Data collection variables included demographics, host risk factors,[7] history of IFI, time between initial oncologic diagnosis or stem cell transplantation and presentation of IFI, antifungal therapy used for fungal prophylaxis prior to IFI diagnosis, duration of steroids prior to fungal diagnosis, duration of neutropenia at time of IFI, primary site of IFI, time between presentation with IFI and identification of organism, surgical interventions to evaluate the presence of IFI, demonstration of fungal elements in tissue/sterile sites, clinical and mycologic criteria for IFI,[7] CAF regimen, initial dose of antifungal prescribed, incidence of TDM, documentation in clinical notes of adverse events, reason for discontinuation of CAF while receiving combination therapy, and mortality at 30 days and 120 days from the time of IFI diagnosis. Two investigators reviewed each chart to determine the classification of IFI. If there was discordance between the classifications, a third investigator reviewed the patient's chart. Mann-Whitney *U* test was used to determine statistical difference in duration of CAF among patients who met criteria for IFI and to determine if TDM impacted duration of CAF. Chi-square test was used to determine if TDM was associated with a difference in the incidence of adverse events.

Results

A total of 57 patients received CAF for 72 separate episodes. One CAF episode was excluded in 1 patient who did not meet European Organization for the Research and Treatment of Cancer criteria for IFI. Seven CAF episodes were excluded because of abnormal liver function tests. Most patients were white males with a median age of 10 years (Table 1). There were 12 patients with 2 CAF episodes and 1 patient with 4 CAF episodes. The median durations of steroid administration and neutropenia prior to fungal diagnosis were 20 days

(range, 1–335 days) and 19 days (range, 1–128 days), respectively. Twenty-one patients had an organism isolated (Table 2). The average time between clinical presentation with IFI and identification of pathogen was 8 days (range, 0–70 days; median, 14 days). The most common pathogen identified in cultures or pathology was *Aspergillus fumigatus*. The most common primary site of IFI was pulmonary (31 of 72 episodes), with many cases involving multifocal infection (26 of 72 episodes; Table 3). Among patients in whom a pathogen was identified, liposomal amphotericin B was the most frequently prescribed antifungal therapy prescribed for CAF (20 of 29 episodes). Overall, voriconazole was frequently prescribed in combination with either micafungin (26 episodes) or liposomal amphotericin B (21 episodes) for IFI (Table 4). Overall, the median duration of CAF was 6 days (range, 3–170 days). Patients who met criteria for proven IFI or probable IFI received a longer duration of CAF in comparison with patients with possible IFI ($p = 0.02$ and 0.04, respectively).

Median initial doses of antifungals prescribed were: voriconazole 16 mg/kg/day (n = 47; range, 4–26 mg/kg/day), liposomal amphotericin B 5 mg/kg/day (n = 41; range, 2–8 mg/kg/day), micafungin 3 mg/kg/day (n = 39; range, 1.4–10 mg/kg/day), posaconazole 7.4 mg/kg/day (n = 9; range, 3.7–18 mg/kg/day), itraconazole 8.3 mg/kg/day (n = 6; range, 4–10.8 mg/kg/day), fluconazole 12 mg/kg/day (n = 3; range, 6.8–12 mg/kg/day), isavuconazole 20 mg/kg/day (n = 2; range, 10–30 mg/kg/day), and conventional amphotericin B 0.75 mg/kg/day (n = 1). A loading dose was prescribed as the initial dose for 29.1% of medications prescribed for CAF (voriconazole, 14 episodes; posaconazole, 4 episodes; itraconazole, 2 episodes; isavuconazole, 1 episode). The median duration of CAF was 6 days regardless of whether a loading dose was prescribed for one of the antifungals prescribed as part of CAF (range, 3–170 days) or maintenance doses of antifungals were prescribed for CAF (range, 3–86 days).

Therapeutic drug monitoring was conducted in 63.8% (46 of 72) of CAF episodes. Forty-five of these CAF episodes consisted of a triazole (voriconazole, 37 episodes; posaconazole, 4 episodes; itraconazole, 4 episodes). Serum micafungin and amphotericin B concentrations were sent for 1 CAF episode. Median time to the first collection of an antifungal concentration after CAF was 5 days (range, 2–43 days). Median initial voriconazole, posaconazole, and itraconazole concentrations were 4.2 mg/L (range, 0.9–23 mg/L), 1.63 mg/L (range, 0.4–1.68 mg/L), and 2.5 mg/L (range, 0.76–3.33 mg/L), respectively.

Target antifungal concentration was documented by the clinician in notes for 10 CAF episodes (8 episodes for voriconazole and 2 episodes for posaconazole). Documented target posaconazole concentration was >1.25 mg/L, and the target voriconazole concentration ranged between 1 and 6 mg/L. Of the 10 CAF episodes, 7 episodes (6 unique patients) achieved targeted concentration with initial dosing regimen (median voriconazole dose, 18 mg/kg/day [range, 4–19.2 mg/kg/day]; median posaconazole dose, 4.1 mg/kg/day [range, 3.7–4.5 mg/kg/day]). The remaining 3 CAF episodes (3 unique patients) had a higher antifungal concentration than the targeted concentration (median voriconazole dose, 18 mg/kg/day [range, 16–18 mg/kg/day]). The median duration of CAF was 5 days among patients in whom TDM was not conducted (range, 3–115 days). A total of 15 CAF episodes of the 26 CAF episodes in which TDM was not conducted included a triazole (voriconazole, 10 episodes; posaconazole, 4 episodes; itraconazole, 1 episode).

Reasons for discontinuation of CAF were documented in clinical notes for 35 episodes. Of these episodes, 74% (26 of 35 CAF episodes) were discontinued after therapeutic antifungal concentrations were achieved (voriconazole, 22; itraconazole, 2; posaconazole, 2). Other reasons for discontinuation of CAF included change to monotherapy antifungal therapy (5 episodes), change in one of the antifungal medications prescribed in CAF therapy (2 episodes), awaiting nonfungal studies (1 episode), and an adverse event to liposomal amphotericin B (1 episode).

A total of 10 patients experienced 14 adverse events (infusion-related reaction [episodes = 4], nephrotoxicity [episodes = 4], electrolyte abnormalities [episodes = 2], rash [episodes = 2], liver dysfunction [episodes = 1], hypersensitivity reaction [episodes = 1]) that were documented as related to antifungal therapy. Three patients experienced multiple adverse events while receiving CAF (infusion-related reaction and electrolyte abnormalities, nephrotoxicity and electrolyte abnormalities, and infusion-related reaction, liver dysfunction, and rash). The occurrence of adverse events during CAF was not statistically different between patients who had TDM performed and those who did not ($p > 0.05$). Patients who received TDM received CAF for a longer duration than patients who did not receive TDM ($p = 0.03$). Invasive fungal infection led to surgical intervention in 23.6% (17 of 72) of CAF episodes. All-cause mortality at 30 days and 120 days from the time of fungal diagnosis was 11% (8 of 72) and 21.8% (14 of 64) of CAF episodes.

Discussion

Our study reported the incidence of CAF among patients with a diagnosis of proven, probable, or possible IFI, with a focus on monitoring and safety events. A retrospective study conducted at 6 medical centers reviewed proven and probable pediatric invasive aspergillosis (IA) cases during nearly a 6-year period and the underlying condition, most frequently isolated pathogen, and site of infection were similar to those for our study population.[11] However, 33.6% (44 of 131 patients) received 2 antifungal agents concurrently, and 45.8% (60 of 131) received 3 or

Table 2. Antifungal Therapy Prescribed and Identified Pathogen

Pathogen (Episodes, Unique Patient)	MIC (mg/L) and Susceptibility*
Aspergillus fumigatus (episodes = 5, n = 4)	Amphotericin B: 1 Isavuconazole: 0.5 Itraconazole: 0.125 Micafungin: ≤0.015 Voriconazole: 0.25
	Amphotericin B: 1 Micafungin: >32 Posaconazole: 0.5 Voriconazole: 1
	Amphotericin B: 1 Micafungin: ≤0.015 Voriconazole: 0.25
	Amphotericin B: 0.5 Micafungin: ≤0.015 Posaconazole: 0.06 Voriconazole: 1
Aspergillus flavus (episodes = 3, n = 2)	Amphotericin B: 1 Voriconazole: 1
	Posaconazole: 0.25 Voriconazole: 1
	Amphotericin B: 0.25 Caspofungin: 0.5 Fluconazole: 2 Flucytosine: 0.5 Itraconazole: >32 Micafungin: ≤0.015 Posaconazole: >32 Voriconazole: 32
Candida tropicalis (episodes = 3, n = 2)	Amphotericin B: 1 Anidulafungin: ≤0.015 (susceptible) Caspofungin: 0.015 (susceptible) Fluconazole: 2 (susceptible) Flucytosine: ≤0.060 (susceptible) Itraconazole: 0.25 (susceptible dose-dependent) Micafungin: 0.015 (susceptible) Posaconazole: 0.25 Voriconazole: 0.25

Table 2. cont'd

Pathogen (Episodes, Unique Patient)	MIC (mg/L) and Susceptibility*
Candida albicans (episodes = 2, n = 1)	Amphotericin B: 1 Caspofungin: 0.06 Fluconazole: 0.5 Flucytosine: 0.5 Itraconazole: 1.2 Micafungin: ≤ 0.015 Posaconazole: 0.06 Voriconazole: 0.03
	Amphotericin B: 1 Anidulafungin: ≤0.015 (susceptible) Caspofungin: 0.06 (susceptible) Fluconazole: 128 (resistant) Flucytosine: ≤0.06 (susceptible) Itraconazole: >16 (resistant) Micafungin: 0.015 (susceptible) Posaconazole: >8 (resistant) Voriconazole: 2 (susceptible dose-dependent)
Candida glabrata (episodes = 1, n = 1)	Amphotericin B: 0.5 Anidulafungin: 0.06 (susceptible) Caspofungin: 0.25 (susceptible) Fluconazole: MIC not provided Flucytosine: 16 Itraconazole: 0.5 Micafungin: 0.12 Posaconazole: 0.5 Voriconazole: 0.5 (susceptible)
Candida krusei (episodes = 1, n = 1)	Amphotericin B: 0.5 Caspofungin: 1 Fluconazole: 2 Flucytosine: 0.12 Itraconazole: 1 Micafungin: 0.5 Posaconazole: 1 Voriconazole: 0.06
Candida parapsilosis (episodes = 2, n = 2)	Amphotericin B: 0.5 Caspofungin: 0.015 Fluconazole: 2 Flucytosine: ≤0.12 Itraconazole: 1 Micafungin: 0.5 Posaconazole: 0.25 Voriconazole: 0.06
Exserohilum rostratum (episodes = 4, n = 1)	Amphotericin B: 0.125 Micafungin: 0.125 Posaconazole: 0.125 Voriconazole: 4
Histoplasma species (episodes = 2, n = 2)	
Zygomycosis (episodes = 2, n = 2)	Amphotericin B: 0.06 Isavuconazole: 1 Posaconazole: 0.125

Table 2. cont'd

Pathogen (Episodes, Unique Patient)	MIC (mg/L) and Susceptibility*
Rhizopus (episodes = 1, n = 1)	
Scedosporium species (episodes = 2, n = 1)	Amphotericin B: 2 Caspofungin: 16 Fluconazole: >32 Flucytosine: >32 Itraconazole: 8 Micafungin: 0.03 Posaconazole: 8 Voriconazole: 1
Alternaria species (episodes = 1, n = 1)	

MIC, minimum inhibitory concentration

* Clinical and Laboratory Standards Institute antifungal susceptibility testing guidelines[10] were referenced to determine and interpret MIC against isolated pathogen. Susceptibility results reported if documented in medical chart.

Table 3. Antifungal Prophylaxis and Invasive Fungal Site of Infection

	Episodes (Total = 72), No. (%) of Unique Patients
Antifungal prophylaxis prior to IFI*	
Fluconazole	7 (12.2)
Micafungin	3 (5.2)
Voriconazole	2 (3.5)
Primary site of infection while receiving CAF†	
Pulmonary	31 (47.3)
Multifocal‡	26 (33.3)
CNS/brain	4 (5.2)
Skin	3 (5.2)
Sinus	2 (3.5)
Blood	2 (3.5)
Bone	1 (1.7)
Other	3 (5.2)

CAF, combination antifungal therapy; IFI, invasive fungal infection

* Antifungal prophylaxis prior to diagnosis of IFI was defined as the number of patients who received antifungal prophylaxis at the time of IFI diagnosis.
† There were 3 unique patients who had multiple CAF episodes who had a diagnosis of either pulmonary or multifocal IFI.
‡ Multifocal disease is defined as IFI identified in multiple sites.

more concurrent antifungal medications for 3 days or more. In addition, even though all patients in our study received CAF, 79% of patients in the aforementioned study received CAF.

A prospective surveillance study conducted from January 2002 through December 2003 investigated the safety and efficacy of caspofungin in combination with other systemic antifungal medications prescribed for treatment of proven or probable IA to pediatric patients with a diagnosis of hematologic or oncologic malganacy.[12] The median duration of CAF was 29 days (range, 3–382 days). For patients who received CAF for at least 7 days, CAF was composed of caspofungin and liposomal amphotericin B (50%; 18 of 36) for a median time of 26 days (range, 7–90 days), caspofungin and voriconazole (25%; 9 of 36) for a median time of 38 days (range, 12–94 days), and the remaining patients received sequentially both combinations for a median time of 19 days (range, 7–84 days).

In comparison with our study, voriconazole was primarily prescribed concomitantly with liposomal amphotericin B or micafungin, and our median duration of CAF was shorter. The difference in CAF may have been due to the time period in which each study was conducted. Voriconazole received FDA approval in May 2002. Thus, the prospective study was underway prior to FDA approval of voriconazole. Therefore, over time, the use of voriconazole for IA has been recommended and could reflect the more prevalent use in our study.[4] Our shorter duration of CAF may be due to the intended purpose for CAF reported by clinicians. Of the episodes in which the reason for discontinuation of CAF was documented, 74% (26 of 35 CAF episodes) were discontinued after therapeutic antifungal concentrations were achieved. Voriconazole was prescribed for 22 of these CAF episodes.

In addition, previous studies have reported that CAF was well tolerated and resulted in no severe renal or liver impairment associated with antifungal use.[12] However, 2 patients discontinued use of voriconazole because of diarrhea and bone pain (n = 1) and bradyarrhythmia (n = 1), and 1 patient experienced transient skin rash while receiving caspofungin that did not result in discontinuation of therapy. Regarding tolerability of CAF in our study, 10 patients experienced a variety of adverse events that were associated with antifungal therapy. These reactions may have occurred while receiving monotherapy; however, prescribing multiple antifungal medications that may have overlapping adverse events may heighten the risk and requires vigilance.

The dose of antifungal therapy prescribed for IFI within our study varied; however, the median doses for conventional and liposomal amphotericin B, micafungin, and fluconazole were comparable to recommended dosing of systemic antifungal agents in pediatric patients.[13] The median dose of voriconazole and itraconazole in our study was slightly higher than the typical dose. Itraconazole has wide interindividual/intraindividual pharmacokinetic variability and has been reported to display variable oral bioavailability based on formulation.[14] Itraconazole solution has a higher bioavailability in fasting state and absorption is not pH dependent, whereas itraconazole capsules require an acidic environment to improve the drug's pharmacokinetic variability and bio-

Table 4. Antifungal Therapy Prescribed and Duration of Combination Antifungal Therapy for Invasive Fungal Infection

Type of IFI (n)	CAF With Liposomal Amphotericin B, No. of Episodes (%)	CAF With Micafungin, No. of Episodes (%)	CAF, Median (IQR), days
Proven (35)	Voriconazole: 12 (34.2) Micafungin: 6 (17.1) Itraconazole: 4 (11.4) Posaconazole: 4 (11.4) Fluconazole: 1 (2.8)	Voriconazole: 5 (14.2) Fluconazole: 1 (2.8) Posaconazole: 1 (2.8) Conventional amphotericin B: 1 (2.8)	8 (5–13.5)
Probable (11)	Voriconazole: 4 (36.3) Itraconazole: 1 (9)	Voriconazole: 6 (54.5)	6 (5.5–14)
Possible (26)	Voriconazole: 5 (19.2) Posaconazole: 3 (11.5)	Voriconazole: 15 (57.6) Isavuconazole: 2 (7.7) Fluconazole: 1 (3.8)	5 (4–6.74)

CAF, Combination Antifungal Therapy

availability. As reported with itraconazole, voriconazole has wide interindividual/intraindividual pharmacokinetics within the pediatric population.[14-16] In addition, younger pediatric patients have been shown to require higher voriconazole doses to achieve a targeted voriconazole concentration.[17-19] The pharmacokinetic parameters of posaconazole differ based on the formulation. Administration of posaconazole suspension with an acidic beverage, after a nutritional supplement, with a high-fat meal or in divided doses increases maximum plasma concentration and area under the concentration time curve.[20] Potent acid suppression associated with proton pump inhibitors, mucositis, or diarrhea can significantly decrease bioavailability of posaconazole suspension.[21] Bioavailability of posaconazole delayed-release tablets is higher than the suspension formulation and is not significantly impacted by food intake.[22,23]

Therapeutic drug monitoring of triazoles in the pediatric population can be helpful because of the pharmacokinetic variability that can impact achieving target antifungal concentrations.[14,15] The optimal triazole concentration and time to obtain these concentrations after initiation of therapy has been established.[14] In our study, TDM was conducted in 63.8% of CAF episodes. The median time to first collection of an antifungal concentration was within the established guidance; however, time to collection ranged widely. Our institute's antimicrobial stewardship handbook provides guidance on when to obtain antifungal concentrations after initiation of therapy, and the goal antifungal concentration. However, the target antifungal concentration was documented in clinical notes in only 14% of CAF episodes in which TDM was conducted. Therapeutic drug monitoring optimizes antifungal dosing and is essential for antimicrobial stewardship.[24] Incorporating TDM among patients prescribed CAF and documentation of target antifungal concentration in clinical notes can facilitate timely attainment of appropriate triazole concentrations and may assist in de-escalating antifungal therapy. Therefore, measures to optimize initial dosing and timely attainment of therapeutic concentrations could lead to shorter duration of CAF.

Our study did include some limitations. Our study was retrospective and was conducted at a single center. A prospective, multicenter study would be helpful to obtain a wider range of patients, determine causality of adverse events due to CAF, and variations in CAF usage. A larger number of patients would potentially allow for a comparator group of patients who were prescribed antifungal monotherapy for a specific fungal or mold infection. Our study did not compare the difference in mortality between monotherapy and CAF, thus the difference in efficacy and clinical outcomes remains unknown. The definition of IFI for our study was based on the classification presented by the 2008 European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group.[7] These definitions were recently revised by the organization in 2019, and definitions for proven, probable and possible IFI were expanded.[25] These revisions could improve specifying the causative fungi/mold and further define patient populations at risk for IFI.

In conclusion, our study reported the incidence of CAF for proven, possible, and probable IFI during a 6-year period. We were able to determine the most frequent CAF regimen prescribed, adverse events documented by clinicians, and the incidence of TDM while a patient was prescribed CAF. The use of CAF presents the opportunity for antimicrobial stewardship interventions, including appropriate scheduling of serum antifungal concentrations, regular monitoring of laboratory values to assess renal and hepatic impairment, and antifungal "time-out" to determine if CAF is necessary and discuss a duration of therapy.

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