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NEPHROLOGY - ORIGINAL PAPER

Micafungin treatment and eradication of candiduria among hospitalized patients

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Abstract
Purpose In high-risk patients, candiduria may be associated with the development of urinary tract infections (UTI) and invasive candidiasis. The triazole antifungals achieve good urine concentrations, but their use is limited by the emergence of non-albicans *Candida* spp. with low-triazole susceptibility. The echinocandins remain fungicidal against many azole-resistant *Candida* spp., but low urine concentrations limit their use. We examined the rates of candiduria elimination in micafungin-treated patients.
Methods This retrospective analysis evaluated consecutive patients with candiduria (1/2008–4/2011) who were treated with micafungin (100 mg/day) and had post-micafungin urine cultures. Patients were deemed to have either candiduria or UTI and were assessed for short-term (within 2 weeks post-micafungin) and long-term (>1 month post-micafungin) urine sterilization.
Results Thirty-three patients meeting our inclusion criteria were identified. Of these, 16 (48 %) were diagnosed with a *Candida* UTI. A total of 25 patients (76 %) had Foley catheters, which were replaced in 11 (44 %) cases. The majority of patients had *Candida albicans* (39 %), but *Candida krusei* and *Candida glabrata* (33 %) were also isolated. Eight patients (24 %) were immunocompromised, and 29 (88 %) received broad-spectrum antibiotics. Rates of urine sterilization during micafungin treatment, 2 weeks after micafungin, and >1 month after micafungin were 81, 78, and 75 %, respectively.
Conclusions Among hospitalized patients with candiduria, micafungin administration was frequently associated with both short- and long-term urine sterilization. This was observed among patients with or without Foley removal and among those with *Candida albicans*, as well as non-albicans *Candida* spp.

Keywords Candiduria · Echinocandin · Micafungin · Urinary tract infections

Abbreviations

AMB	Amphotericin B
CFU	Colony-forming units
UTI	Urinary tract infections

Introduction

Urinary tract infections (UTI) are the most commonly reported nosocomial infections [1]. Although most UTI are of bacterial origin, nearly 12 % of positive urine cultures in hospitalized patients yield a fungal pathogen [2, 3]. *Candida* spp. represent the most common fungi causing hospital-acquired UTI [4]. The existence of *Candida* spp. in urine cultures poses an interesting diagnostic and therapeutic dilemma, as candiduria may be indicative of a wide range of potential conditions, such as contamination, colonization, or even invasive candidiasis. Common risk factors for candiduria include urinary tract drainage

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devices, recent broad-spectrum antibiotic exposure, immunosuppression, intensive care unit admission, diabetes mellitus, abnormal urinary tract pathology, and malignancy. Candiduria is common among hospitalized patients [4, 5]. An observational study from Europe found that, in hospitalized patients, *Candida* spp. were the third most common organism isolated from the urine [6]. However, over the past decade, there has been a shift in the epidemiology of the *Candida* spp. with an increase in the frequency of UTI from non-albicans *Candida* spp. possessing decreased susceptibility to triazole antifungals [4]. Some have reported that 30–50 % of *Candida* urinary isolates belong to non-albicans species [2, 4, 6–8].

Management of candiduria remains contentious, mainly due to uncertainties surrounding the need to initiate pharmacotherapy or manage patients conservatively. The echinocandin antifungals represent a class of antimicrobials with fungicidal activity against *Candida* spp. and favorable adverse event and drug–drug interaction profiles. However, all agents in this class are minimally concentrated in the urine; caspofungin 1.4 %, micafungin 0.7 %, and anidulafungin <0.1 % [9]. Given the concern over the ability of these agents to achieve therapeutic antifungal concentrations in the urine, the echinocandins have generally been avoided for the management of candiduria. Nevertheless, there is emerging human and animal data documenting that these agents may provide benefit for patients with positive *Candida* urine cultures [10–13]. Herein, we describe our analysis of 33 patients who received micafungin therapy for either candiduria or UTI caused by *Candida* spp. Our objective was to assess the urine sterilization rate on patients under short- and long-term micafungin treatment.

Materials and methods

Study design

This retrospective analysis completed in two tertiary-care academic medical centers evaluated a cohort of consecutive patients managed between January 1, 2008 and April 30, 2011, with candiduria or *Candida* UTI who were treated with micafungin and had follow-up urine fungal cultures available. The primary endpoint was an analysis of the incidence of urine sterilization during the course of micafungin therapy, within two weeks of treatment (e.g., short-term) and greater than one month after treatment (long-term). This study was approved by our institutional review boards as a retrospective analysis; therefore, informed consent was not required. Inpatient and outpatient medical records, including clinic notes, laboratory, and microbiological data and medication histories were reviewed for demographics, hospitalization characteristics, morbidities, antibiotic exposure, microbiologic results, and presence and removal of Foley catheters. All medical records were reviewed by an experienced researcher.

Patients and intervention

A search of the microbiology records was conducted to identify patients with at least one positive urine culture for *Candida* spp. A cross-referencing of these patients with inpatient pharmacy records was completed to discover all patients who were treated with micafungin. Patients with candiduria who received at least one dose of micafungin and had follow-up urine cultures after completion of micafungin therapy were included in this analysis. Patient characteristics are described in Table 1. All patients received 100 mg/day of intravenous micafungin.

Clinical definitions

Clinical practice with regard to the diagnosis of *Candida* spp. was similar between the institutions. Candiduria was defined as a urine culture growing *Candida* spp. at $\geq 10^5$ colony-forming units (CFU)/mL. A *Candida* UTI was defined as *Candida* growth in the urine ($\geq 10^5$ CFU/mL) along with a positive urinalysis and clinical UTI symptoms.

Statistical analysis

Categorical variables were analyzed using Chi-square. The Student's *t* test was used to compare means of continuous variables (SAS 9.2; Cary, NC). Differences were considered significant at *p* values of <0.05.

Table 1 Patient characteristics

Patient characteristic ($N = 33$)	
Mean age (SD)	60 years (19.9)
Female	20/33 (61 %)
Leukemia/lymphoma	6/33 (18 %)
Solid cancer	7/33 (21 %)
Solid organ transplant recipient	2/33 (6 %)
Diabetes mellitus	11/33 (33 %)
Pharmacologically immunocompromised	8/33 (24 %)
Cardiovascular disease	10/33 (30 %)
Chronic lung disease	6/33 (18 %)
Chronic liver disease	1/33 (3 %)
Chronic kidney disease	6/33 (18 %)

Results

Patient characteristics

Thirty-three patients were eligible for and included in our analysis. The group consisted of 20 (61 %) females, with an overall mean age of 60 years. The mean time to the first positive urine culture with *Candida* spp. following hospital admission was 9 days, with a range of 0–47 days. Overall, 25 patients (76 %) had indwelling Foley catheters, which were replaced in only 11 (44 %) cases. Eight patients (24 %) were pharmacologically immunosuppressed, and 29 (88 %) had received or were receiving broad-spectrum antibiotics within 7 days. The mean number of days from first diagnosis of candiduria until micafungin initiation was 4 days, with a range of 0–12 days.

Urine cultures and fungal isolates

Cultures were obtained from Foley catheters in 16 patients (48 %). Overall, the diagnosis of *Candida* UTI was made in 16 (48 %) patients. In addition to candiduria or *Candida* UTI, 11 (33 %) patients had *Candida* growing from clinical cultures obtained from other, non-urologic, sites, with three (10 %) patients also having concomitant *Candida* blood stream infections. The *Candida* isolates included *C. albicans* ($n = 13$; 39 %), *C. glabrata* ($n = 10$; 30 %), *C. parapsilosis* ($n = 2$; 6 %), *C. tropicalis* ($n = 2$; 6 %), *C. krusei* ($n = 1$; 3 %), and *Candida* non-albicans ($n = 5$; 16 %).

Efficacy analysis

When evaluating the primary endpoint, the rates of urine sterilization in those while receiving micafungin treatment, two weeks after micafungin therapy and greater than one month after completion of micafungin therapy, were 81, 78, and 75 %, respectively. Rates of short-term *Candida* eradication among those with Foley catheter replacement was numerically lower, but not statistically significant compared to those without replacement (67 vs. 91 %; $p = 0.18$). The overall rates of eradication among patients with *C. albicans* was comparable to those patients with either *C. glabrata* or *C. krusei* (92 vs. 78 %; $p = 0.37$). The mean and median micafungin treatment duration were 12.5 and 6.0 days, respectively. Please refer Table 2 for a detailed overview of the treatment success by patient characteristics.

Discussion

The existence of *Candida* spp. in the urine poses a significant dilemma when managing hospitalized patients. Most patients with candiduria are asymptomatic, in which case the isolate simply represents contamination or colonization. While there often is trepidation that candiduria predisposes patients to candidemia, this is untrue in the general population [5]. The Infectious Disease Society of America candidiasis guidelines have made recommendations for the proper management of both asymptomatic and symptomatic candiduria [14]. In patients with asymptomatic candiduria, treatment is not warranted, unless the patients belong to a group at high-risk for dissemination, which includes neutropenic patients, those undergoing urologic manipulations and low-birth weight neonates. In patients with symptomatic candiduria, pharmacologic management is recommended. Therapeutic options for *Candida* spp. include amphotericin B (AMB; both deoxycholate and the lipid preparations), flucytosine, triazoles, and echinocandin antifungals [15]. In patients with a triazole-resistant organisms, it is recommended that intravenous AMB deoxycholate with or without flucytosine be considered. The use of AMB bladder irrigation is associated funguria clearance; however, it has been shown that this effect is transient. The lipid-based AMB formulations do not achieve adequate concentrations in the urine; therefore, they are not recommended to manage *Candida* UTI. The newer generation triazoles (i.e., voriconazole, posaconazole, isavuconazole) have provided no further advantage in the management of candiduria given their low urinary concentrations [5]. For circumstances where urine cultures reveal resistant *Candida* spp. in patients at risk for dissemination, there is an urgent need to identify new treatment options for the effective management of candiduria.

The role of the echinocandin antifungals in the management of candiduria remains unclear. Small case series have noted some success with these agents, although failures have also been documented. In an analysis of six patients with significant candiduria, Sobel et al. described successful management of candiduria using caspofungin [11]. Despite the success in this report, others have reported failure with caspofungin when treating *Candida glabrata* UTI [16]. Lagrotteria et al. described a case series of three patients with *Candida glabrata* or azole-resistant *Candida albicans* candiduria effectively managed with micafungin [12]. Pieralli and colleagues describe the successful treatment of *Candida glabrata* urinary sepsis and candiduria with micafungin [13]. In guidelines published by Fisher et al., both caspofungin and anidulafungin are included in treatment algorithms for the management of asymptomatic candiduria only in the presence of evidence of disseminated candidiasis, but not recommended for management of symptomatic candiduria [15].

It was with some of this information that we have undertaken the largest analysis to date evaluating an echinocandin for management of candiduria and *Candida* UTI. In our analysis of 33 patients, we demonstrated excellent

Table 2 Treatment success by patient characteristics

	Candiduria eradicated while on micafungin			Candiduria: short-term eradication			Candiduria: long-term eradication		
	Yes *n* (%) [SD]	No *n* (%)	*p* value[1]	Yes *n* (%) [SD]	No *n* (%)	*p* value	Yes *n* (%) [SD]	No *n* (%)	*p* value
Age	53.8 [19.4]	42 (58.0)	0.87	61 [17.9]	64 [13.0]	0.74	61 [18.1]	74 [10.1]	0.27
Female	10 (77)	0 (0)	0.63	16 (55)	4 (100)	0.12	12 (60)	2 (67)	0.99
Hospital days pre-candiduria	9.6 [11.7]	6.0 (7.1)	0.66	7.8 [11.5]	8.0 [11.1]	0.98	7.7 [13.6]	5.0 [5.3]	0.73
Clean catch culture (VS Foley cultures)	1 (50)	7 (54)	0.92	14 (48)	2 (50)	0.95	8 (40)	3 (100)	0.09
Candida albicans (VS non-albicans)	4 (31)	1 (50)	0.59	12 (41)	1 (25)	0.88	7 (35)	0 (0)	0.53
Candida growing in non-urine sites	1 (8)	1 (50)	0.10	8 (28)	3 (75)	0.10	6 (30)	2 (67)	0.27
Interval from candiduria diagnosis to micafungin initiation	4.4 [4.5]	5.5 (0.7)	0.72	4.0 [3.8]	4.0 [4.5]	0.99	4.6 [4.0]	1.7 [2.9]	0.28
Days of micafungin prior to F/U culture	5.1 [3.3]	0.5 (2.1)	0.14	12.6 [16.6]	12.3 [9.8]	0.97	17. [18.5]	6.3 [7.6]	0.45
Foley replaced	10 (91)	1 (100)	0.92	16 (67)	3 (75)	0.81	11 (58)	3 (100)	0.27
Exposure to broad antibiotics	13 (100)	1 (50)	0.13	24 (83)	4 (100)	0.50	17 (87)	3 (100)	0.99
Underlying comorbidities									
Diabetes mellitus	3 (23)	0 (0)	0.63	10 (34)	1 (25)	0.82	8 (40)	0 (0)	0.53
Immunocompromised	3 (23)	0 (0)	0.45	8 (28)	0 (0)	0.31	6 (30)	1 (33)	0.98
Cardiovascular disease	3 (20)	1 (50)	0.42	13 (45)	3 (75)	0.28	10 (50)	1 (33)	0.99
Chronic lung disease	2 (15.4)	0 (0)	0.55	6 (21)	0 (0)	0.43	6 (30)	0 (0)	0.54
CKD	6 (46)	0 (0)	0.21	6 (21)	0 (0)	0.43	4 (20)	0 (0)	0.97

[1] Categorical variables: by Fisher exact test, continuos variables: by Logistic regression

short- and long-term eradication of the *Candida* spp. in patients treated with micafungin 100 mg/day. Despite low urine concentrations, micafungin distributes rapidly and moderately into renal tissues, which is likely the explanation for its effectiveness [17–19]. Of particular interest was the efficacy of micafungin against both *Candida glabrata* and *Candida krusei*. Both of these *Candida* spp. represent organisms with either inherited or innate fluconazole resistance, and the ability to eradicate these organisms in the urine with micafungin is likely a function of its potent fungicidal activity in the renal tissue.

We acknowledge the limitations of our analysis. Our data were collected in a retrospective manner. We relied on local diagnostic criteria, laboratory data, and microbiologic outcomes evaluation, which may have varied slightly between the two centers.

Management of candiduria is a clinical challenge, and symptomatic candiduria may represent a complicated UTI in a number of at-risk patients. Notwithstanding its low urinary concentrations, micafungin does distribute well to renal tissue and the bladder. Its tissue penetration, along with its fungicidal mechanism of action, may play an important role in the management candiduria. Among hospitalized patients with candiduria, micafungin, administered at 100 mg/day, was frequently associated with both short-term and long-term urine sterilization. This was observed among patients with or without Foley catheter removal/replacement and among those with *Candida albicans* as well as non-albicans *Candida* spp.

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Compliance with ethical standards

Conflict of interest Drs. Golan and Gabardi have received research funding support from Astellas Pharma US; Anisa Mohammed and Drs. Sura and Martin have no conflicts of interest to report.

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