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Micafungin in the treatment of candiduria: A case series

Lauren E. Kane, Katie M. Muzevich *

Department of Pharmacy, VCU Health, Richmond, VA, United States

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ABSTRACT

Echinocandin antifungal agents are not routinely recommended for the treatment of candiduria due to low urine concentrations and a paucity of clinical data supporting this indication. This report presents five cases describing the use of micafungin for the treatment of candiduria. Each patient received parenteral micafungin for a minimum of 6 days and had resolution of baseline fungal within 30 days of treatment completion.

1. Introduction

The presence of yeast in urine is common among intensive care unit (ICU) patients, particularly among those who have predisposing risk factors such as catheterization, antimicrobial exposure, diabetes mellitus, and immunosuppression [1]. Current estimates indicate that up to 22% of patients in the ICU will have a urine culture positive for yeast during their hospitalization [2]. However, the clinical significance of this positive culture can often be confounded by contamination and colonization [3]. Nonetheless, the decision to treat is especially important, as candiduria in critically ill patients may be the only indication of disseminated candidiasis [4]. Although guidelines have been published, controversies over the diagnosis and management of candiduria still persist due to the difficulty in recognizing the clinical implications and significance of yeast in urine [5].

Historically, drug selection for the treatment of candiduria has been less controversial than that of diagnosis due to the limited number of antifungal agents achieving adequate urine concentrations. Fluconazole, an azole antifungal agent, is the preferred therapy for fluconazole-susceptible organisms because of its ability to achieve high urine concentrations and its favorable safety and pharmacokinetic profile [5]. However, isolates of the second most common causative species of candiduria, *Candida glabrata,* have demonstrated increased resistance to fluconazole [2,6,7].

The echinocandin class of antifungal agents represents an alternative therapy that possesses activity against most *Candida* species including fluconazole-resistant species of *C. glabrata* [8]. Currently, due to a paucity of clinical data and poor glomerular filtration, echinocandins are typically excluded as an antifungal agent used in the treatment of candiduria. However, pharmacokinetic and tissue distribution models in animals indicate micafungin penetrates into renal tissue [9–11]. In both single and multiple-dose studies evaluating the tissue distribution of micafungin in animals, micafungin was shown to rapidly and moderately distribute into liver, spleen, and kidney tissue [9]. In the multiple-dose study, renal tissue concentrations were noted to be in several-fold excess of the MIC_{90} of the *Candida* and *Aspergillus* species tested [10]. Despite moderate distribution into the kidneys, echinocandins exhibit negligible concentrations ($<2\%$) of intact drug in human urine [12,13]. Existing literature supporting the use of echinocandins for candiduria is limited to three reports containing ten individual cases in humans [14–16].

The first case series by Sobel et al. was a retrospective review of six patients with symptomatic candiduria who had received caspofungin in phase II or III clinical studies. All patients had clearance of candiduria after receiving of at least seven days of caspofungin for the treatment of complicated urinary tract infections caused by *Candida* species. Three cases were persistent urinary tract infections secondary to *C. glabrata* in patients with diabetes mellitus and either urinary obstruction or stasis. The remaining three cases of candiduria were secondary to hematogenous renal candidiasis in patients with candidemia [14]. Lagrotteria et al. described the successful use of micafungin therapy in the treatment of two cases of persistent *C. glabrata* and one case of fluconazole-resistant *Candida albicans* candiduria in immunocompromised patients [15]. The final case report describes a

* Corresponding author.
E-mail address: Katie.muzevich@vcuhealth.org (K.M. Muzevich).

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Table 1
Patient characteristics of patients with candiduria treated with micafungin.

Patient	Age	Gender	Candida species	Catheter at time of first culture	Catheter change	Persistent candiduria following catheter change[a]	Fungemia[b]	Outcome Of candiduria
1	64	Male	*Candida glabrata*	Yes	Yes	Yes	No	Cleared
2	78	Female	*Candida glabrata*	No	–	–	No	Cleared
3	42	Female	*Candida glabrata*	Yes	Yes	Yes	No	Cleared
4	60	Female	*Candida albicans*	Yes	Yes	Yes	No	Cleared
5	55	Female	*Candida glabrata*	Yes	Yes	Yes	No	Cleared

[a] Persistence was defined as an absence of the clearance of yeast on a repeat urinalysis or urine culture.
[b] Candidemia was defined as a positive blood culture or positive Beta-D-glucan test.

Table 2
Initial Urinalysis characteristics of patients with candiduria treated with micafungin.

Patient	Leukocyte Esterase	Nitrite	RBC/HPF	WBC/HPF	Epithelial Cell/HPF	Hyaline Cast/LPF	Bacteria	Other
1[a]	Negative	Negative	3	2	1	6	Few	Budding yeast
2	Large	Negative	0–3	50–100	0–5	None	Few/HPF	
3	Small	Negative	Occasional	0–5	0–5	2–5	Few	0–1/LPF coarse granular casts
4	Moderate	Negative	Field obscured	Present	None	None	Present/HPF	Budding yeast
5	No initial urinalysis							

HPF = high powered field.
[a] Initial UA from hospital day 19 prior to catheter change.

favorable response to micafungin in the treatment of *C. glabrata* urinary sepsis in a diabetic patient with renal insufficiency [16]. This report aims to add to the current literature by describing the results of five patients who had resolution of candiduria following receipt of micafungin therapy (Tables 1 and 2).

This was a retrospective medical record review of adult patients admitted to an ICU with a urine culture positive for at least 100,000 colonies of yeast treated with micafungin monotherapy from January 1, 2012 to October 31, 2014. All subjects were patients at Virginia Commonwealth University Health System (VCUHS), a 755-bed tertiary academic medical center in Richmond, Virginia. This study was reviewed and approved by the VCU Health Institutional Review Board. Micafungin was the echinocandin antifungal agent on formulary at the time of study.

Patients were identified by a query of the health system's electronic medical system (Cerner Information Systems). A total of 158 patients had a urine culture positive for yeast during the study period. Patients were then excluded if they received an antifungal regimen other than micafungin monotherapy, had an unknown treatment outcome, a polymicrobial urinary tract infection, or were a prisoner or pregnant. Five cases were identified; each patient received at least six days of parenteral micafungin therapy and had resolution of baseline fungal positivity within 30 days of treatment assessed via repeat urinalysis or urine culture. A detailed description of these five patient cases are included below.

2. Patient cases

2.1. Patient 1

A 64-year old male with history of chronic obstructive pulmonary disease and esophageal stricture with chronic percutaneous endoscopic gastrostomy (PEG) tube was initially admitted as a transfer from an outside hospital after he developed septic shock from *Clostridium difficile* following dilation of an esophageal stricture. Upon admission, he underwent a total colectomy with eventual ileostomy creation and abdominal closure. His postoperative recovery was complicated by vancomycin-resistant enterococcal bacteremia, Methicillin-Resistant Staphylococcus aureus (MRSA) pneumonia resulting in respiratory failure requiring mechanical ventilation, and a *C. glabrata* urinary tract infection. An initial urine culture on hospital day 19 revealed 60×10^4 CFU/L of *C. glabrata*. Following a change of his catheter, the patient had two subsequent urine cultures with $> 10 \times 10^5$ CFU/L and 80×10^4CFU/L of *C. glabrata* on day+23 and day+24, respectively. A computerized axial tomography scan of the abdomen and pelvis at this time revealed mild bladder wall thickening likely exaggerated by underdistension. However, a superimposed infection could not be ruled out. On day+26, due to concerns for clinical decompensation with persistent leukocytosis, a rising serum creatinine, hypotension requiring vasopressor support, and tachypnea, micafungin 100 mg daily intravenously (IV) was started. Fungal blood cultures were negative and patient was continued on micafungin for 14 days with eradication of candiduria upon completion of treatment. Shortly thereafter, the patient was transitioned to comfort care measures.

2.2. Patient 2

A 78-year old female with history of diabetes and heart failure was admitted for septic shock two days after being discharged from a prolonged hospitalization for acute cardiac ischemia requiring stent placement that was complicated by a left femoral vascular injury. Upon initial presentation, she was febrile (T_{max}: 40.1 °C), tachycardic (HR:100 beats per minute), tachypneic (RR:22 breaths per minute) and developed hypotension that required vasopressor support. Possible sources of sepsis included a left groin surgical wound and a urinary tract infection based on a urinalysis that revealed large leukocyte esterase, 50–100 WBC/hpf, few bacteria, and budding yeast. The urine culture subsequently grew $> 10 \times 10^5$ CFU/L *C. glabrata*. The patient completed a 10 day course of micafungin 100 mg daily for her urinary tract infection and a 14 day course of meropenem for wound tissue cultures that revealed *Escherichia coli* and *Proteus mirabilis* with intermittent requirement of vasopressor support. A urine culture upon