



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.

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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 MIC₉₀ 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).

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	<i>Candida glabrata</i>	Yes	Yes	Yes	No	Cleared
2	78	Female	<i>Candida glabrata</i>	No	–	–	No	Cleared
3	42	Female	<i>Candida glabrata</i>	Yes	Yes	Yes	No	Cleared
4	60	Female	<i>Candida albicans</i>	Yes	Yes	Yes	No	Cleared
5	55	Female	<i>Candida glabrata</i>	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 80×10^4 CFU/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

completion of therapy indicated clearance of candiduria. Shortly thereafter, due to declining mental status, the decision was made to refrain from escalation of care and the patient passed away.

2.3. Patient 3

A 42-year old female with micronutrient deficiency secondary to gastric bypass surgery was initially admitted for polyneuropathy. During the hospitalization, she developed hypoxemic respiratory failure presumed to be secondary to pneumonia with super-imposed pulmonary edema. On day +6, despite the receipt of broad-spectrum antibiotics, her oxygenation status continued to worsen. She was started on micafungin due to concern for disseminated fungemia as she had both a respiratory culture revealing yeast and a urine culture with $> 10 \times 10^5$ CFU/L *C. glabrata*. The following day, her catheter was changed and a repeat urinalysis revealed persistent candiduria. After six days of micafungin treatment, her urine culture was negative for yeast. She was continued on micafungin for a total of 12 days for candiduria and was never found to be fungemic. Unfortunately, despite aggressive care her clinical status deteriorated and the decision was made to withdraw care.

2.4. Patient 4

A 60-year-old female with a past medical history significant for coronary artery disease, heart failure, and atrial fibrillation was initially admitted for dyspnea requiring intubation. On day +19, she became febrile (T_{\max} : 39.3 °C), tachycardic (HR: 138 beats per minute), and tachypneic (RR: 23 breaths per minute); respiratory cultures were positive for yeast and a repeat urine culture following a catheter change revealed $> 10 \times 10^5$ CFU/L *Candida albicans*. She was started on micafungin 100 mg daily due to concerns for disseminated candidiasis. Blood cultures remained negative and she completed a seven-day course of micafungin. A urine culture obtained on day +26 revealed no significant growth of yeast.

2.5. Patient 5

A 55-year old female with hepatitis B and C, HIV with an undetectable viral load, diabetes mellitus, coronary artery disease, and end-stage renal disease was initially admitted secondary to concerns for a mediastinal abscess after recent coronary artery bypass graft surgery and a sternal wound infection. On day +5, a urine culture revealed $> 10 \times 10^5$ CFU/L *C. glabrata*. Her catheter was replaced and a new urine culture was drawn on day +8. This culture demonstrated persistence of $> 10 \times 10^5$ CFU/L *C. glabrata* with an MIC of ≥ 32 µg/ml. Micafungin 100 mg daily was stated and continued for 10 days. A urine culture at the end of treatment showed no growth [17].

3. Discussion

Guideline-based treatment for symptomatic candiduria includes amphotericin B, fluconazole and flucytosine [5]. The use of amphotericin B has routinely been limited due to issues with tolerability and the potential for nephrotoxicity. Of concern with the use of fluconazole is the increasing incidence of azole-resistant non-*albicans* species of *Candida*. Flucytosine may be an option in this subset of resistant infections. However, renal insufficiency especially among critically ill patients may limit flucytosine's usefulness.

Echinocandins represent an attractive treatment option in this setting given their favorable safety profile, broad-spectrum of

activity against *Candida* species, limited drug interactions, and lack of dose adjustments in renal insufficiency [18]. Unlike fluconazole, echinocandins, including micafungin, have activity against biofilm produced by *Candida albicans* [19–21]. This may be of particular benefit, as one study investigating candiduria in catheter-associated urinary tract infections found that more than half of the of *Candida* isolates produced biofilm [17]. Major concerns with the use of echinocandins in the treatment of candiduria are their inability to achieve adequate urine concentrations and increasing resistance to *C. glabrata* species [12,13,22,23]. Despite this, data from these five cases add to the existing evidence that micafungin may be successful in eradicating candiduria [11,15,16].

This study is not without limitations. First, all patients who had an unknown treatment outcome or who received combination therapy were excluded. Combination antifungal therapy was defined as concomitant or sequential therapy with more than one antifungal agent. Due to this exclusion criterion, it is possible that patients who received micafungin but were then switched to an alternative agent secondary to treatment failure were excluded. Thus, this case series may lack critical information on scenarios in which micafungin was an ineffective treatment for candiduria.

Secondly, the majority of patients in this study had an indwelling catheter at the time of the positive urine culture. Candiduria in this setting commonly represents colonization and thus treatment would only be indicated if the patient was symptomatic or candiduria persisted despite the removal of predisposing factors [4]. Due to the retrospective nature of this study, it was not possible to assess if patients were symptomatic. However, all patients with indwelling catheters had persistent candiduria despite a catheter change. In the single patient who did not have a catheter, the initial urinalysis revealed pyuria. If pyuria is utilized as a surrogate marker for infection, this case may be representative of a true urinary tract infection. Despite the limitation of not being able to confirm if these cases were true infections, micafungin did result in the short-term clearance of yeast in all five cases. Unfortunately, information on long-term urine sterilization was unable to be obtained.

Finally, this report is limited by a small sample size. Many patients were excluded due to receipt of a guideline-recommended antifungal agent, fluconazole. While some of the patients excluded received as few as one dose of fluconazole, the authors felt that inclusion of these cases could be confounded by co-administration of an antifungal agent with good urinary concentrations. Despite these limitations, the results support the use of micafungin for the treatment of candiduria. However, the results of this study should be interpreted with caution until these findings are confirmed by a prospective, randomized controlled trial.

Conflict of interest

There are no conflicts of interest.

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