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Case report

Outcomes of caspofungin use in the treatment of *Candida*-related urinary tract infections, a case series

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ABSTRACT

Echinocandins are generally excluded in the treatment of *Candida*-related urinary tract infections due to their poor urinary concentration. In the presence of fluconazole resistant *Candida* species, such as *C. Glabrata* and *C. auris*, alternative therapies are needed. We herein report the use of caspofungin for the treatment of 10 patients with candiduria, including *C. auris*. Mycological cure was achieved in 6 of 7 patients and clinical cure was achieved in 8 of 10 patients. Larger studies are needed to confirm our findings.

Background

Cystitis caused by *Candida* is common in hospitalized patients [1]. The distinction between asymptomatic candiduria and *Candida* cystitis is not always straightforward, and when treatment is deemed appropriate, selecting the optimal antifungal therapy may be challenging. Oftentimes, candiduria represents colonization and requires no treatment. Diligence in assessing the likelihood of a true *Candida* cystitis should be practiced to avoid unnecessary treatment [1,2]. When the decision is made to treat a candiduria, drug selection is dependent on pharmacokinetics, fungal strain and anatomical site [1–4]. Fluconazole is typically the drug of choice for *Candida* cystitis on the basis of strong efficacy and favorable pharmacokinetics [2]. Of the *Candida* species, previous epidemiological data demonstrated a higher prevalence of *C. albicans* (40–65%), *C. tropicalis* and *C. parapsilosis* implicated in urinary tract infections [1,5] – fluconazole traditionally offers adequate coverage for these *Candida* species. However, there has been an increasing prevalence of fluconazole-resistant *albicans* strains as well as a rise in non-*albicans* strains which are implicated in nosocomial infections [1,3,5–8]. More recent distribution of *Candida* isolates in urinary tract infections depicts a higher prevalence of *C. glabrata* and *C. krusei* , which fluconazole offers little to no coverage of [5,8].

As such, there is a need to identify safe and effective alternative treatments for *Candida* cystitis/pyelonephritis in cases where fluconazole cannot be used. Although echinocandins achieve low urinary concentration, there are several case reports of successful clinical outcomes when used for the treatment of *Candida* urinary tract infections (UTIs) [3,9–11]. The purpose of this study to identify the clinical and mycological cure rates of caspofungin for *Candida*-related urinary tract infections at our quaternary care institution.

Methods

We conducted a retrospective cohort study at a quaternary care hospital between January 2016 and October 2019. This retrospective review was conducted at the Cleveland Clinic in Abu Dhabi, United Arab Emirates. The study protocol was reviewed and approved by the institution's Research Ethic Board. Participants were included in the study based on the following criteria: age greater than 18 years, admitted to hospital and having a positive urine culture for any *Candida* species within 14 days of initiation of caspofungin. Exclusion criteria consisted of the following: the presence of an ileal conduit, kidney stones, pregnancy or recent urostomy (within 30 days). Baseline demographics and clinical data were obtained from the patients' electronic medical records. Pertinent baseline variables that were collected included the presence of indwelling catheters, duration of catheter insertion prior to

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urine culture, presence of immunocompromising illness, urologic or prostate abnormalities, nephrolithiasis, congenital abnormalities of the urinary tract, critical care admission, prolonged hospitalization (greater than 7 days) and *Candida* species. Prevalence rates were reported using descriptive statistics for baseline demographics as well as for the primary and secondary outcomes.

Cystitis was defined as *Candida* growth from a urinary culture and at least one of the following: dysuria, frequency or urgency. A complicated cystitis was defined as cystitis and at least one of the following risk factors: male, obstruction, immunocompromised, renal failure, renal transplant, neurogenic bladder, presence of an indwelling catheter or presence of renal calculi. A pyelonephritis was defined as *Candida* growth from a urinary culture and at least two of the following: fever, flank pain or costovertebral tenderness, leukocytosis, WBC casts in urine or symptoms of cystitis. Lastly, a catheter-associated urinary tract infection was defined as the presence of an indwelling urinary catheter with signs and symptoms of UTI, and or the presence of *Candida* growth in a single catheter urine specimen or midstream urine, despite removal of the catheter in the previous 48 h.

The primary outcome of mycological cure was defined as the eradication of *Candida* species on a repeat urine culture. Secondary outcomes included clinical cure (defined as defervescence, hemodynamic stability, resolution of urinary symptoms, if present, and normalization of WBCs within 72 h) and the recurrence of a positive *Candida* culture, of the same species, within up to 90 days.

Identification of *Candida* species in the laboratory was performed using Vitek2 and Vitek MS automated instruments (Biomerieux, France). Antifungal susceptibility testing was performed using Vitek 2 AST-YS08 susceptibility card. CLSI breakpoints were used for susceptibility interpretations for all *Candida* species except for *Candida auris*, where tentative CDC breakpoints were used.

Results

A total of 10 patients were included in this chart review. Seven of them were admitted to the intensive care unit at the time of infection and 3 patients were admitted to an acute care unit. Eight patients had indwelling Foley catheters at the time of infection, which were exchanged or removed after starting caspofungin. Six patients had a catheter-associated *Candida* cystitis, 3 had a *Candida* pyelonephritis and 1 had asymptomatic candiduria. Of note, no patients had candidemia. The sample mean age was 66 $\pm$ 11 years, 5 of whom were female. Further, 8 patients were immunocompromised (6 of whom were receiving immunosuppressive therapy, one transplanted and one receiving chemotherapy) and all patients were diabetic. Three patients had benign prostatic hyperplasia and one patient had bilateral nephrostomy tubes in place at the time of the treatment. *Candida* species prevalence included the following: *C. auris* (caspofungin susceptible) in 5 patients, *C. glabrata* in 2 patients, *C. lusitaniae* in 1 patient, *C. albicans* in 1 patient and unspecified yeast in 1 patient.

Of the 10 patients, 6 had a fungal load greater than 100,000 CFU/mL; pyuria was present in 7 patients. Caspofungin was administered as 70 mg intravenously once followed by 50 mg intravenously daily, with a mean treatment duration of 7 $\pm$ 2 days. Of the 7 subjects who had a repeat urine culture, the primary outcome of mycological cure was achieved in 6/7 patients (85%); the repeat culture was done within 7 $\pm$ 2 days after therapy initiation. Clinical cure was achieved in 8/10 patients (90%). Recurrence of cystitis within 90 days occurred in 4/8 patients (50%).

Discussion

Our findings describe the successful outcomes of utilizing caspofungin in the management of *Candida*-related urinary tract infections. Our sample encompassed a range of patients including those with catheter-related urinary tract infections, immunocompromised patients and patients with fever and hemodynamic instability. With increasing rates of resistance and the rise of non-albicans strains, alternative options are needed to treat urinary tract infections caused by resistant *Candida* species. Given the lack of robust data supporting the efficacy of echinocandins for the treatment of urinary tract infections, clinical practice guidelines have not advocated for their use for this particular indication [2].

To our knowledge, the largest study to date examining the use of caspofungin for UTIs, retrospectively included 6 patients whom were successfully treated (3 of which were secondary to hematogenous spread, and 3 were secondary to an ascending infection) [3]. Of the echinocandin class, there is presently more data supporting the use of micafungin for the treatment of *Candida*-related urinary tract infections. A study by Gabardi et al. retrospectively analyzed 33 patients using micafungin for the treatment of *Candida* UTI, demonstrating successful urinary sterilization for short and long term outcomes [11]. Similarly, Grau et al. described the successful use of micafungin for the treatment of *Candida*-related UTIs, of which 5 of the 6 were cystitis [10].

Urothelial infections (urethra and bladder) are usually superficial with a potential to invade the bladder wall while pyelonephritis is typically thought of as a renal parenchymal infection [12] As such, the treatment of cystitis and urethritis traditionally involves utilizing an antibiotic that is renally excreted to ensure eradication of the organism at the level of the surface mucosa.There is increasing evidence showing that high drug urinary excretion may not be required for the treatment of UTIs; pyelonephritis or otherwise [11]. It is thought that renal parenchymal and epithelial cells achieve adequate free drug concentrations through systemic absorption, which may be sufficient to treat urinary tract infections [12,13]. Our findings concur with other studies that demonstrate urinary fungal clearance when using echinocandins despite their low urinary excretion.

Free antimicrobials (unbound to protein) can move freely across different body fluid compartments including uroepithelial cells and intracellular and extracellular compartments, which may provide sufficient antimicrobial levels to treat superficial urotherlial infections and parenchymal kidney infections alike [13,14]. Serum-free drug concentration of antimicrobials can be used as an indicator and/or surrogate of tissue concentration when deciding on breakpoints of antimicrobials [13]. Our clinical and microbiologic cure rates suggest that therapeutic echinocandins‘ levels may have been achieved at the urothelial tissue level and could potentially be considered for the treatment of urinary tract infections despite their poor renal excretion. Echinocandins have a wider antifungal spectrum, are well tolerated and generally have fewer drug-drug interactions, making them an ideal alternative to manage resistant *Candida,* and particularly in immunocompromised patients.

The limitations of our study were inherent to its retrospective nature, small sample size and being a single-center study.

Conclusion

Caspofungin may achieve clinical and micrologic cure in the treatment of urinary tract infections caused by various *Candida* species. It may be a safe and effective alternative to azoles for the treatment of urinary infections in the case of resistant *Candida* strains, azole intolerance or where drug-drug interactions is of concern. Larger multicenter studies are needed before the widespread adoption of echinocandins for urinary infections can occur.

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Ethical approval

Cleveland Clinic Abu Dhabi Ethics Research Committee approval was granted before initiating data collection. Consent was waived given

the retrospective nature of the study.

Consent

NA.

CRediT authorship contribution statement

Laila Rkieh: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Supervision. **Wasim El Nekidy:** Methodology, Writing – original draft, Formal analysis, Writing – review & editing, Supervision. **Leen Oyoun Alsoud:** Formal analysis, Data curation, Writing – review & editing. **Adnan Alatoom:** Conceptualization, Methodology, Writing – review & editing. **Rania El Lababidi:** Conceptualization, Methodology, Writing – review & editing. **Mohamad Mooty:** Conceptualization, Methodology, Writing – review & editing. **Ahmad R. Nusair:** Conceptualization, Methodology, Writing – review & editing.

Conflicts of interest

All authors declare no potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

References

[1] Fisher JF, Sobel JD, Kauffman CA, Newman CA. Candida urinary tract infections–treatment. Clin Infect Dis 2011;52(Suppl. 6):S457–66. https://doi.org/10.1093/cid/cir112 [PMID: 21498839].

[2] Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of Candidiasis: 2016 update by the infectious diseases society of America. Clin Infect Dis 2016;62(4):e1–50. https://doi.org/10.1093/cid/civ933 [Epub 2015 Dec 16. PMID: 26679628; PMCID: PMC4725385].

[3] Sobel JD, Bradshaw SK, Lipka CJ, Kartsonis NA. Caspofungin in the treatment of symptomatic candiduria. Clin Infect Dis 2007;44(5):e46–9. https://doi.org/10.1086/510432 [Epub 2007 Jan 22. PMID: 17278048].

[4] Alfouzan WA, Dhar R. Candiduria: evidence-based approach to management, are we there yet? J Mycol Med 2017;27(3):293–302. https://doi.org/10.1016/j.mycmed.2017.04.005 [Epub 2017 May 10. PMID: 28501465].

[5] Gajdács M, Dóczi I, Ábrók M, Lázár A, Burián K. Epidemiology of candiduria and Candida urinary tract infections in inpatients and outpatients: results from a 10-year retrospective survey. Cent Eur J Urol 2019;72(2):209–14. https://doi.org/10.5173/ceju.2019.1909 [Epub 2019 Jun 29. PMID: 31482032; PMCID: PMC6715075].

[6] Osawa K, Shigemura K, Yoshida H, Fujisawa M, Arakawa S. Candida urinary tract infection and Candida species susceptibilities to antifungal agents. J Antibiot 2013;66(11):651–4. https://doi.org/10.1038/ja.2013.68 [Epub 2013 Jun 26. PMID: 23801184].

[7] Aubron C, Suzuki S, Glassford NJ, Garcia-Alvarez M, Howden BP, Bellomo R. The epidemiology of bacteriuria and candiduria in critically ill patients. Epidemiol Infect 2015;143(3):653–62. https://doi.org/10.1017/S0950268814000934 [Epub 2014 Apr 24. PMID: 24762978].

[8] Yashavanth R, Shiju MP, Bhaskar UA, Ronald R, Anita KB. Candiduria: prevalence and trends in antifungal susceptibility in a tertiary care hospital of mangalore. J Clin Diagn Res 2013;7(11):2459–61. https://doi.org/10.7860/JCDR/2013/6298.3578 [Epub 2013 Nov 10. PMID: 24392372; PMCID: PMC3879894].

[9] Schelenz S, Ross CN. Limitations of caspofungin in the treatment of obstructive pyonephrosis due to Candida glabrata infection. BMC Infect Dis 2006;6:126. https://doi.org/10.1186/1471-2334-6-126 [PMID: 16895593; PMCID: PMC1560384].

[10] Grau S, Luque S, Echeverría-Esnal D, Sorlí L, Campillo N, Montero M, et al. Urinary micafungin levels are sufficient to treat urinary tract infections caused by Candida spp. Int J Antimicrob Agents 2016;48(2):212–4. https://doi.org/10.1016/j.ijantimicag.2016.05.010 [Epub 2016 Jul 5. PMID: 27424599].

[11] Gabardi S, Martin S, Sura M, Mohammed A, Golan Y. Micafungin treatment and eradication of candiduria among hospitalized patients. Int Urol Nephrol 2016;48(11):1881–5. https://doi.org/10.1007/s11255-016-1410-0 [Epub 2016 Sep 1. PMID: 27587066].

[12] El Nekidy WS, Soong D, Mooty M, Ghazi IM. Treatment of recurrent urinary tract infections in anuric hemodialysis patient, do we really need antimicrobial urinary concentration? IDCases 2020;20:e00748. https://doi.org/10.1016/j.idcr.2020.e00748 [PMID: 32274331; PMCID: PMC7132144].

[13] Gilbert DN. Urinary tract infections in patients with chronic renal insufficiency. Clin J Am Soc Nephrol 2006;1(2):327–31. https://doi.org/10.2215/CJN.01931105 [Epub 2006 Jan 11. PMID: 17699224].

[14] Mouton JW, Theuretzbacher U, Craig WA, Tulkens PM, Derendorf H, Cars O. Tissue concentrations: do we ever learn? J Antimicrob Chemother 2008;61(2):235–7. https://doi.org/10.1093/jac/dkm476 [Epub 2007 Dec 6. PMID: 18065413].