

## CASE STUDIES IN CANDIDIASIS\*

Jack D. Sobel, MD<sup>†</sup>ABSTRACT

The number of antifungal agents currently available to treat different forms of candidiasis has grown enormously. Most *Candida* infections are uncomplicated, and the choice of antifungal agent is usually straightforward. However, complicated candidiasis infections do occur, and the 2 case studies discussed in this article review the considerations that need to be made when choosing therapy under these circumstances. Case study 1 describes a candiduric patient and highlights the importance of localizing the site of infection, which will help determine the need for and selection of therapy. Case study 2 describes a patient with candidal endocarditis, in whom surgical interventions must be considered as first-line therapy, and the choice of fungicidal agent may depend on more than just the minimum inhibitory concentration for the organism. (*Adv Stud Med.* 2006;6(6C):S538-S540)

**CASE STUDY 1: CANDIDURIA***PRESENTATION*

FO is a 78-year-old man referred from his urologist because of recurrent *Candida* urinary tract infections. He is currently asymptomatic.

*PAST MEDICAL HISTORY*

The letter from the urologist states that FO suffers from urinary papillomatosis confined to the bladder mucosa. The urologist also reports that, in the past, the patient has had frequency, dysuria, and hematuria. Multiple urine cultures have been positive for a single *Candida* species, *Candida glabrata*. Past treatment with itraconazole has not been successful, and the urologist has had to use bladder irrigation with amphotericin B to control the infection. In addition, FO has a history of type 2 diabetes.

*LABORATORY STUDIES*

Urine cultures are positive for *C glabrata*, and there is marked pyuria. His creatinine is 1.7 mg/dL, and the creatinine clearance is less than 30 mL/minute.

*MANAGEMENT*

Because the patient was asymptomatic, we elected not to treat him. However, FO returned 2 months later, this time describing 2 to 3 weeks of dysuria, hematuria, and severe flank pain. He had a fever of 102°F. He was being treated by his urologist with fluconazole 200 mg/day; he said this has improved his symptoms slightly. On examination FO had renal angle tenderness. Urinalysis revealed pyuria and budding yeast, but no bacteriuria. Blood cultures were drawn. Ultrasound showed bilateral upper tract dilation.

FO was admitted to the hospital and treated with intravenous caspofungin for 10 days. He promptly deeffervesced. His dysuria and flank pain resolved. His urine cultures were negative and have remained negative since.

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## DISCUSSION

Some clinicians may have been surprised by the choice of caspofungin in this case because it is poorly excreted into the urine. We had numerous other options to consider. Fluconazole is the single most important and useful antifungal agent for treating urinary tract *Candida* and other fungal infections because of its penetration into the urine, and the high concentrations that can be achieved. However, FO had already failed fluconazole treatment. In fact, given the patient's prior treatment history, this case would likely warrant susceptibility testing when making the treatment decision. Voriconazole, in contrast to fluconazole, is active against most *C glabrata* species, although approximately 5% are still resistant. However, voriconazole is not excreted in the urine, even if renal function is normal, thus it was not an option for FO. Likewise, itraconazole is not excreted into the urine. Little is known about the pharmacokinetics of intravenous amphotericin B. However, its nephrotoxicity is well established, thus it would not be a good choice in this case. The lipid formulation avoids much of the nephrotoxicity, but the very mechanism by which the lipid formulations reduce nephrotoxicity prevents them from being excreted in the urine. Therefore, in most patients with candiduria, amphotericin B lipid complex is not a preferred drug. Flucytosine penetrates well into the urine, and most *C glabrata* isolates are sensitive to flucytosine. However, if flucytosine is administered in the presence of renal failure, the clinician must be willing to obtain serum drug levels and to monitor for potential toxicity. Flucytosine would have been an appropriate choice for FO.

The use of amphotericin B bladder irrigation has been disputed in the past few years. Drew et al suggest that amphotericin B irrigation does not have any diagnostic or therapeutic value for funguria.<sup>1</sup> In the case of FO, the high fever and renal angle tenderness suggested the he most likely had pyelonephritis from *C glabrata*, as opposed to a bladder infection, so that bladder irrigation would not be very useful. Nephrostomy tubes may have been a consideration, but more diagnostic studies would be needed to determine their appropriateness in this case.

Caspofungin was chosen to treat FO, even though less than 1% is excreted into the urine. Caspofungin was effective because this was a parenchymal bladder infection, not a superficial infection from catheter colonization. Caspofungin was not treating infected urine; it was treating the infected urinary tract. FO

had pyelonephritis, and caspofungin achieves high concentrations in the kidney. Also, with papillomatosis, he had parenchymal involvement of the bladder. Caspofungin is able to achieve high concentrations in tissue and thus was able to resolve the infection.

Infectious diseases specialists continue to encounter many patients with candiduria. The majority of these patients have long-term indwelling catheters and are colonized with *Candida*, but do not require therapy. They are able to bypass therapy because, in the absence of stasis or obstruction, ascending infections occur in less than 3% of colonized patients.<sup>2</sup> Unfortunately, many of these patients are treated unnecessarily. With a candiduric patient, the clinician should attempt to localize the site of infection and to assess whether it is symptomatic to determine whether the patient requires therapy.

## CASE STUDY 2: *CANDIDA PARAPSILOSIS*

### PRESENTATION

AP is a 51-year-old man who was admitted to the hospital with fever.<sup>3</sup> He was status post-prosthetic aortic valve replacement 7 months prior. His blood cultures were positive for *Candida parapsilosis*.

### MANAGEMENT

The cardiac surgeons were hesitant to remove the valve, and the patient himself refused to undergo any additional cardiac surgical procedures.

AP was placed on amphotericin B (0.7 mg/kg/day) and flucytosine (25 mg/kg every 6 hours). After 7 days, his blood cultures cleared, but he rapidly (and predictably) developed progressive renal insufficiency. He was then placed on combination antifungal therapy: intravenous (IV) caspofungin (50 mg/day) and IV fluconazole (400 mg/day).

AP completed 6 weeks of combination therapy. His blood cultures remained clear and he was discharged on lifetime treatment with oral fluconazole 400 mg/day.

### CLINICAL COURSE

AP returned 3 months later with fever, chills, and blood cultures positive for *C parapsilosis*. Fluconazole was discontinued, and he was started immediately on IV caspofungin 50 mg/day. Despite 10 days of treatment, his blood cultures remained positive. Susceptibility showed multiazole and multiechinocandin resistance (Table).<sup>3</sup> Resistance had developed to micafungin and voriconazole without exposure. Interestingly, the organism remained susceptible to

anidulafungin and amphotericin B.

AP was treated with amphotericin B lipid complex (5 mg/kg/day); after 1 week, he de-effervesced. He remained afebrile with negative blood cultures on that regimen, but ultimately died for unrelated reasons.

#### DISCUSSION

The decision to treat AP with such a high dose of fluconazole (400 mg/day) was surprising, given his renal insufficiency. *C parapsilosis* is highly susceptible to fluconazole. In the case of AP, fluconazole was part of a combination regimen, and may not have been necessary.

As the authors of this case study note, “the most significant factor that should have been considered in this case is the fact that the optimal management of this patient should have been surgical removal of the infected prosthetic valve, followed by prolonged antifungal therapy.”<sup>3</sup> *Candida* endocarditis remains a surgical disease. Although we may hear or read about anecdotal cases of *Candida* endocarditis that were treated and cured by medical therapy alone, these are exceptional. Whenever possible, surgery—together with antifungal therapy—should be the treatment.

Both echinocandins and polyenes are rapidly cidal, and they are the first-line treatments of potential endocarditis. There may be a role for combination therapy in patients in whom surgery is not possible, but, cur-

rently, combination antifungal therapy for candidiasis syndromes is rarely indicated.

Interestingly, in vitro susceptibility tests of *Candida* species for echinocandins show that the minimum inhibitory concentrations (MICs) are significantly higher for *parapsilosis* than they are for *albicans*, *glabrata*, and *tropicalis*.<sup>4,6</sup> However, the clinical significance of these higher MICs is not yet clear. In randomized, controlled studies, patients with *C parapsilosis* and treated with echinocandins have done just as well when compared to the comparator arm.<sup>7-9</sup> Therefore, *C parapsilosis* should not be considered a contraindication for echinocandin therapy in the usual cases of candidemia. For unique cases, such as this case, susceptibility tests should be performed and followed when deciding on a treatment regimen.

#### REFERENCES

1. Drew RH, Arthur RR, Perfect JR. Is it time to abandon the use of amphotericin B bladder irrigation? *Clin Infect Dis*. 2005;40:1465-1470.
2. Ang BS, Telenti A, King B, et al. Candidemia from a urinary tract source: microbiological aspects and clinical significance. *Clin Infect Dis*. 1993;17:662-666.
3. Moudgal V, Little T, Boikov D, Vazquez JA. Multiechinocandin- and multiazole-resistant *Candida parapsilosis* isolates serially obtained during therapy for prosthetic valve endocarditis. *Antimicrob Agents Chemother*. 2005;49:767-769.
4. Pfaller MA, Boyken L, Hollis RJ, et al. In vitro activities of anidulafungin against more than 2500 clinical isolates of *Candida* spp, including 315 isolates resistant to fluconazole. *J Clin Microbiol*. 2005;43:5425-5427.
5. Espinell-Hingroff A. In vitro antifungal activities of anidulafungin and micafungin, licensed agents and the investigational triazole posaconazole as determined by NCCLS methods for 12,052 fungal isolates: review of the literature. *Rev Iberoam Micol*. 2003;20:121-136.
6. Pfaller MA, Boyken L, Hollis RM, et al. In vitro susceptibilities of *Candida* spp. to caspofungin: four years of global surveillance. *J Clin Microbiol*. 2006;44:760-763.
7. Colombo AL, Perfect J, DiNubile M, et al. Global distribution and outcomes for *Candida* species causing invasive candidiasis: results from an international randomized double-blind study of caspofungin versus amphotericin B for the treatment of invasive candidiasis. *Eur J Clin Microbiol Infect Dis*. 2003;22:470-474.
8. Ostrosky-Zeichner L, Kontoyiannis D, Raffalli J, et al. International, open-label, noncomparative, clinical trial of micafungin alone and in combination for treatment of newly diagnosed and refractory candidemia. *Eur J Clin Microbiol Infect Dis*. 2005;24:654-661.
9. Pfaller MA, Diekema DJ, Boyken L, et al. Effectiveness of anidulafungin in eradicating *Candida* species in invasive candidiasis. *Antimicrob Agents Chemother*. 2005;49:4795-4797.

Table. MIC Results

	First Admission	Second Admission
Fluconazole	1.0	>64
Voriconazole	0.03	>16
Caspofungin	2	>16
Micafungin	8	>16
Anidulafungin	1	2
Amphotericin B	0.25	0.5

MICs are expressed as µg/mL.

Interpretive criteria for susceptibility (breakpoints) to fluconazole: <8 µg/mL, susceptible; 16 to 32 µg/mL, dose-dependent susceptible; >64 µg/mL, resistant. Interpretive criteria for voriconazole, caspofungin, micafungin, anidulafungin, and amphotericin B have not been developed. However, the susceptibility breakpoints for voriconazole and amphotericin B are considered to be <1 µg/mL.

For the echinocandins, the MICs for 90% of the *Candida* strains tested are between 0.01 and 2 µg/mL.

MIC = minimum inhibitory concentration.

Adapted with permission from Moudgal et al. *Antimicrob Agents Chemother*. 2005;49:767-769.<sup>3</sup>