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Case report

# A case of recurrent *Candida glabrata* fungemia and successful treatment with rezafungin

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ABSTRACT

Antifungal resistance in *Candida glabrata* can develop to different classes of drugs, including the azoles and echinocandins. This organism is known to cause infective endocarditis with a particular predilection for prosthetic valves. Herein we present a case of recurrent fungemia with *C. glabrata* in a middle-aged woman with Tetralogy of Fallot who had a right ventricle to pulmonary artery conduit, and a transcatheter pulmonary valve replacement in the past. Her isolate showed increasing minimum inhibitory concentrations (MIC) to various antifungals with higher MICs to azoles, including resistance to fluconazole, resulting in limited treatment options. She had affliction of her prosthetic pulmonic valve with *C. glabrata* and was treated with the second-generation echinocandin, rezafungin, for six months. This case illustrates the tolerability profile of long-term treatment with rezafungin.

## Case report

### *Introduction*

*Candida glabrata*, also known as *Nakaseomyces glabratus*, is known to cause life-threatening fungemia and can spread to different parts of the body, with a particular preference for heart valves [1]. Individuals with prosthetic valves are at a higher risk of developing infective endocarditis due to this pathogen [1]. Treating endocarditis caused by *C. glabrata* is challenging primarily because the pathogen tends to form biofilms, allowing it to adhere to the surface of the valves persistently [1]. This leads to a tenacious infectious condition for which optimal therapy is through surgical valve resection and replacement in conjunction with antifungal medications [2]. Additionally, the resistance patterns exhibited by *C. glabrata* make managing this condition more complicated. Fluconazole resistance is encountered amongst some *C. glabrata* isolates, and against these strains the newer azoles have reduced activity [2].

We report a case of *Candida glabrata* fungemia with recurrence, resulting in pulmonic bioprosthetic valve endocarditis. The patient had limited treatment options, so treatment was instituted with the once weekly echinocandin antifungal, rezafungin. This is the first case of long-term successful use of rezafungin for endocarditis reported in the literature in the United States, and also serves to highlight the drug's tolerability. Six months of therapy were well tolerated with no evidence of recurrence in the four months of follow-up after discontinuation of therapy.

### Case

A 50-year-old woman weighing 90.4 kg, with BMI of 34 kg/m$^2$, with well-controlled diabetes, hypothyroidism, coronary artery disease, congenital Tetralogy of Fallot (TOF), a history of atrial flutter and inducible monomorphic ventricular tachycardia, with dual chamber implantable cardioverter defibrillator (ICD) implantation, had recurrent candidemia, and we outline her presentation herein. She underwent TOF correction with pulmonary valve replacement at six years of age. At age 15, she received a right ventricle to pulmonary artery (RV to PA)

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conduit. Later, at 44 years of age, she underwent a transcatheter pulmonary valve replacement due to recurrent pulmonary valve regurgitation. In early 2023, she experienced abdominal and lower back pain and was found to have a bloodstream infection with *Candida glabrata* for 72 h. The isolate had a minimum inhibitory concentration (MIC) of <=0.008 μg/ml for micafungin, and 4 μg/ml for fluconazole. The blood cultures on day 4 of a recent admission were negative. A computed tomography (CT) scan of the abdomen and pelvis revealed no abnormalities except for a mobile redundant sigmoid colon with slight internal rotation about the mesocolon. A transesophageal echocardiogram (TEE) did not identify valvular vegetations. A formal ophthalmologic evaluation was not done but no visual symptoms were reported. An Indium-111 tagged white blood cell scan showed no abnormal activity. The minimal volvulus of the intestine was reasoned to be the cause of fungemia, causing the translocation of *C. glabrata* from the intestinal wall to the bloodstream. General surgery consultation was obtained, and no intervention was deemed necessary. She was monitored clinically and discharged after completion of two weeks of intravenous micafungin. Three months later, she returned to the emergency room with a similar abdominal pain and was found to have recurrent *C. glabrata* candidemia for 48 h. The isolate had an MIC of <=0.06 μg/ml for micafungin, and 8 μg/ml for fluconazole, indicating increasing MICs to these antifungals over time. A repeat CT scan of the abdomen and pelvis showed no pathology. Repeat blood cultures on day three of admission were negative. She had vegetations on her ICD leads and on her bioprosthetic pulmonic (Melody) valve. She was treated for *C. glabrata* infective endocarditis with intravenous micafungin 100 mg once daily for six weeks and thereafter, transitioned to oral voriconazole 200 mg twice daily. The choice to continue suppressive treatment was favored since she had prosthesis involvement with no surgical intervention undertaken.

One month later, she underwent elective ICD explantation as a result of her infectious complication and was continued on voriconazole because of as-yet unresolved pulmonic vegetations. She was on voriconazole for a total of two months when she was admitted due to shortness of breath and was found to have recurrent *C. glabrata* candidemia. A voriconazole trough was checked and noted to be 1.09 μg/ml. A TEE showed an overriding RV to PA conduit with a bioprosthetic valve, which was calcified with vegetations, alongside severe pulmonic stenosis and moderate-to-severe pulmonary insufficiency. She remained persistently fungemic for a total of twelve days. Susceptibility testing for the initial blood culture isolates notably differed from the day ten blood culture isolate, showcasing higher MICs to multiple antifungals, including expanded spectrum azoles (Table 1). As a result of persistent candidemia, source control with surgical intervention was pursued and she underwent a repair of TOF, right pulmonary arterioplasty, replacement of pulmonary valved conduit with homograft, excision of infected ventricular septal defect (VSD) patch, debridement of calcified patch areas, and right ventricular outflow tract cryoablation of conal areas to either side of her VSD patch. Following surgical excision, the valve was tested. The results indicated even higher MICs for most antifungals compared to the blood culture isolates (Table 1). Susceptibility testing was requested for ibrexafungerp and rezafungin (UT Health San Antonio Fungus Testing Laboratory), and low MICs for these therapeutic agents were noted. Initially, the patient received a three-month course of IV micafungin 100 mg once daily. A repeat transthoracic echocardiogram at two months no longer revealed pulmonary valvular vegetations.

The patient's recurrent infection with *C. glabrata* prompted a decision to pursue long-term treatment aimed at preventing infection recurrence. Due to concerns regarding the prior instance of voriconazole suppression despite which recalcitrant fungemia ensued and escalating MICs to other azoles amongst the *C. glabrata* isolates, there was a reluctance to consider azoles as a viable long-term therapeutic option. Although micafungin had effectively demonstrated its ability to suppress the infection, its once-daily dosing regimen necessitated the use of a peripherally inserted central catheter (PICC) for the duration of treatment, which posed potential risks.

Subsequently, the patient was transitioned to weekly rezafungin (400 mg IV for the first dose and 200 mg weekly thereafter), administered via a peripheral intravenous venous line placed for the duration of each infusion. Monthly safety monitoring through laboratory tests, to include complete blood counts and comprehensive metabolic panels, revealed no abnormalities. The patient was evaluated at clinic follow-up after one month on rezafungin, and no concerns were identified. The patient completed treatment with rezafungin for a total duration of six months. Following treatment with six months of rezafungin, the patient opted to stop and clinically monitor for symptoms. A C-reactive protein was notably negative. She was advised to get blood cultures. However, she only obtained testing three months after completion of therapy. Blood cultures were negative. She had episodes of ventricular tachycardia and was scheduled to undergo a right ventricular outflow tract cryoablation. As further precaution, prior to the cryoablation, she underwent workup with metagenomic sequencing of plasma microbial cell-free DNA test (Karius®), and no microbes were detected at statistically significant levels on metagenomic sequencing. She remains clinically well six months following discontinuation of therapy.

**Table 1**
Day one, day seven, and day ten blood culture during most recent admission (third recurrence) of *C. glabrata* fungemia; and pulmonary valve culture *Candida glabrata* isolate MIC in μg/ml, with interpretation of MIC included within parenthesis.

| Antifungal | Day 1 | Day 7 | Day 10 | Pulmonary valve culture isolate |
|---|---|---|---|---|
| Fluorocytosine | - | <=0.06 (NIB) | - | <=0.06 (NIB) |
| Amphotericin B | - | 0.5 (NIB) | 1 (NIB) | 2 (NIB) |
| Anidulafungin | - | 0.06 (S) | 0.03 (S) | 0.12 (S) |
| Caspofungin | - | 0.06 (S) | 0.06 (S) | 0.12 (S) |
| Fluconazole | 4 (S-dd) | 8 (S-dd) | 8 (S-dd) | 64 (R) |
| Itraconazole | - | 0.5 (NIB) | 0.25 (NIB) | 2 (NIB) |
| Micafungin | 0.03 (S) | 0.015 (S) | 0.015 (S) | 0.03 (S) |
| Posaconazole | - | 0.5 (NIB) | 1 (NIB) | 2 (NIB) |
| Voriconazole | 0.12 (NIB) | 0.25 (NIB) | 0.25 (NIB) | 2 (NIB) |
| Ibrexafungerp | - | - | - | 0.25 (NIB) |
| Rezafungin | - | - | - | 0.125 (S) |

Minimum Inhibitory Concentration (MIC); Susceptible-dose-dependent (S-dd); No Interpretive Breakpoint (NIB); Susceptible (S); Resistant (R).

## Discussion

Invasive candidiasis and candidal endocarditis have a high degree of morbidity and mortality [1,2]. *Candida* spp. are the most common cause of fungal endocarditis, with non-albicans species causing rising infections [3]. *Candida albicans* is the leading cause of bloodstream infections [2]. In a study of 164 patients, *C. albicans* was implicated in 36.2 %, and *C. parapsilosis* complex 34.4 % of endocarditis cases, constituting the majority of *Candida* spp. causing endocarditis [4]. The predilection of *Candida* spp. to adhere to epithelial surfaces, cardiac valves, and prosthetic material to form extracellular biofilms makes the presence of a prosthetic valve a risk factor for the acquisition of Candida endocarditis [1], an important cause of severe and recurrent infections in our case. *Candida glabrata* (*Nakaseomyces glabratus*) comprises 4–9 % of cases of Candida endocarditis [1]. The recommended treatment for *Candida* endocarditis is valve replacement followed by antifungal therapy, which results in a decrease in mortality [1–3]. In the event valve replacement cannot be performed, long-term antifungal treatment is recommended [1–3]. Combination antifungal therapy did not have a significant mortality benefit compared to monotherapy with an antifungal agent [3]. When our case patient was initially diagnosed with *Candida* endocarditis, she was treated with antifungal therapy alone and

relapsed. Recurrence of candidemia ensued and valve replacement strategy was pursued at a later date. The 2016 Clinical Practice Guidelines for the management of candidiasis recommend removing implantable cardiac defibrillators, generator pockets, and ventricular assist devices have patients undergo valve replacements [2]. Treatment should then continue for at least six weeks after surgery, or longer in patients with perivalvular abscesses or other complications. For patients who cannot undergo valve replacement therapy, long-term suppression with fluconazole is recommended [2]. We decided to treat our patient for a longer duration given the complexity, the high mortality rate associated with the disease, and her history of recurrent Candidemia.

Rezafungin is a weekly infusion echinocandin, which represents an innovative approach to treating refractory candidiasis. Unlike the daily administration required by other available echinocandins (micafungin, caspofungin, and anidulafungin), rezafungin offers the convenience of once-weekly dosing. This dosing strategy provides unique opportunities for the medication to be used for outpatient parenteral antimicrobial therapy (OPAT). This medication avoids a PICC line for home or facility administration and can instead be administered in an infusion center. This allows those requiring OPAT to avoid PICC line placement and saves the cost of home health or skilled nursing facility placement [5–7]. A phase 3 clinical trial involved 199 patients and compared rezafungin versus caspofungin in patients with candidemia and invasive candidiasis. This trial excluded patients with the following conditions, septic arthritis in a prosthetic joint, osteomyelitis, and myocarditis, meningitis, chorioretinitis, any CNS infection, chronic disseminated candidiasis, or endocarditis. Efficacy and safety results were comparable between the two groups [8]. Due to approval of rezafungin being several years after publication, the current Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Management of Candidiasis updated in 2016 does not address the specific place in therapy for rezafungin [2]. In these guidelines, echinocandins as a class are recommended as first line therapy for the initial treatment of candidemia. The echinocandins are also recommended as a treatment option for suspected or confirmed invasive candidiasis in a variety of infectious sites outside of the central nervous system per the IDSA guidelines [2]. Currently, long-term echinocandin therapy is typically reserved for patients with contraindications to the use of azoles. This may include patients with QTc prolongation, major drug interactions, or resistance to azole therapy, or ineffective treatment with azoles, such as our patient. Real world data with rezafungin use has been described in a few instances in Italy. The first instance was in a 70-year-old woman with *C. glabrata* fungemia and native aortic valve endocarditis, who was treated with six weeks of rezafungin, during which time there was a gradual reduction in ß-D-glucan values, later turning negative [9]. Later, two additional cases in a patient with sacro-coccygeal osteomyelitis secondary to *C. tropicalis* and *C. glabrata* treated with eight weeks of rezafungin, and in a patient with *C. tropicalis* fungemia, prosthetic aortic valve endocarditis, and Thoracic Endovascular Aortic Repair (TEVAR) without the possibility of further surgical interventions, treated with six months of rezafungin have been reported [10]. No adverse events were reported in these cases [9,10].

Our institution and reference lab both utilize Clinical Laboratory Standards Institute (CLSI) breakpoints found in the CLSI MM27M44S document, which includes published breakpoints for *C. glabrata* with anidulafungin, caspofungin, micafungin, rezafungin, fluconazole, and voriconazole [11]. In vitro susceptibility testing can vary between laboratories, leading to variable minimum inhibitory concentration (MIC) results, as seen with our *C. glabrata* isolate (Table 1). *Candida glabrata*'s primary resistance mechanism to azoles involves the overexpression of CDR1 and CDR2, affecting the efflux pump. Higher triazole dosing can overcome this, but only fluconazole has specific dose recommendations for susceptible dose-dependent breakpoint, even though this is a class effect for *C. glabrata* [11]. While MICs to azoles to certain *Candida* spp. are gradually increasing, the number of *C. glabrata* isolates resistant to azoles remains similar for the past 20 years [12–14].

Rezafungin's mechanism of action involves inhibiting the 1,3-beta-D-glucan synthase enzyme complex found in fungal cell walls, leading to osmotic instability and fungal cell death. Notably, this enzyme complex is essential for fungal viability but absent in mammalian cells [7]. Rezafungin exhibits concentration-dependent fungicidal activity against *Candida* species, with MICs similar to other echinocandins. However, certain *Candida* spp., such as *C. parapsilosis*, *Meyerozyma guilliermondii* (formally *Candida guilliermondii*), and *C. lusitaniae*, display intrinsic reduced echinocandin susceptibility. Reduced echinocandin susceptibility is predominantly caused by mutations in the glucan synthase catalytic subunit-encoding *FKS* genes (*FKS1* and *FKS2*) that affect specific regions on the Fks protein (Fks1p and Fks2p, respectively) called hot spot regions [15]. For *C. glabrata,* the presence of a mutation at one or both hot spot regions in either Fks1p or Fks2p is a risk factor for treatment failure [15]. We could only predict this mutation through phenotypically measuring the isolates' MIC. *FKS* mutations that affect the other echinocandins also confer resistance to rezafungin; however, the relevance of the reduced susceptibility to clinical outcomes has not been established for rezafungin [8].

Amphotericin deoxycholate and azoles have demonstrated decreased activity against *Candida* biofilms compared to echinocandins, showing poor penetration into vegetations [16,17]. In contrast, both echinocandins and lipid formulations of amphotericin have shown more potent activity against *Candida* biofilms. However, there is significantly more published literature on echinocandins, including prospective, open-label clinical trials, cohort studies, and several case reports [2]. Additionally, the side effect profile of echinocandins is considerably more favorable compared to liposomal amphotericin [1]. Liposomal amphotericin can cause electrolyte abnormalities, including hypocalcemia, hypokalemia, hypomagnesemia, and hyponatremia, which may lead to cardiac arrhythmias and rhabdomyolysis. It is also associated with nephrotoxicity and immediate infusion-related non-anaphylactic reactions that require premedication and ongoing monitoring [5]. Therefore, amphotericin is not an ideal choice for OPAT due to its side effect profile and the need for increased monitoring. We chose rezafungin over liposomal amphotericin for our patient as salvage therapy due to the more extensive literature supporting echinocandins for reducing biofilm formation and lower risk of adverse drug reactions.

In conclusion, treatment with rezafungin proved to be beneficial for our complicated patient following valve replacement. Long term usage of rezafungin did not reveal any adverse effects in our case.

## CRediT authorship contribution statement

**Thomas F. Patterson:** Writing – review & editing, Funding acquisition. **Kristi Traugott:** Writing – review & editing. **Samantha Aguilar:** Writing – review & editing, Writing – original draft, Data curation. **Divya Chandramohan:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Nathan P. Wiederhold:** Writing – review & editing. **Gerard Gawrys:** Writing – review & editing.

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

## Ethical approval

The patient was treated with the standard of care. No research studies were conducted. Thus, the study does not require Institutional Review Board Approval.

## Institutional Review Board Statement

Ethical review and approval were waived for this study because the patient received standard of care only and written informed consent was obtained from the patient.

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## Declaration of Competing Interest

Patterson TF: Received research support to University of Texas Health San Antonio, TX or has served as a consultant to Basilea Pharmaceutica, Cidara Therapeutics, Inc., Elion Therapeutics, F2G Ltd, Gilead Sciences, Inc., and SCYNEXIS, Inc.

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