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Treatment of *Candida Glabrata* With Micafungin: A Case Report and Brief Review of the Literature

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Abstract

We report the case of a patient with multiple *Candida* bloodstream infections post emergency laparotomy, Hartmann's procedure, abdominal closure and drainage. The patient also experienced recurrent central venous catheter *Candida* infections. The treatment of *Candida tropicalis* bloodstream infection with fluconazole and caspofungin was initially successful; however the patient consequently developed *Candida glabrata* bloodstream infection which did not respond to therapy with fluconazole or caspofungin. Although at the time of treatment of this patient, the *C. glabrata* strain was considered to be susceptible to caspofungin, the new clinical breakpoints recently published by the Clinical and Laboratory Standards Institute show that this strain was in fact resistant to caspofungin. The patient was successfully treated with micafungin and a line lock was used for the Hickman line. This case study is the first documented European case report of successful treatment of breakthrough *C. glabrata* blood stream infection with micafungin.

Keywords: *Candida glabrata*; Echinocandins; Treatment; Microbial sensitivity tests; Disease management

Introduction

The risk factors for invasive candidiasis include antibiotic use and duration, more than 4 days on intensive care or longer than 48 hours on mechanical ventilation, high APACHE II score, abdominal surgery, total parenteral nutrition (TPN), central venous catheter (CVC) in situ, and concomitant infection [1, 2]. Around 60% of patients will have one or more of these risk factors [3]. The epidemiology of *Candida* bloodstream infection is changing, as most invasive fungal infec-

tions previously caused by *C. albicans*, are now increasingly caused by *C. glabrata*, *C. parapsilosis* and *C. krusei* [3]. The change in the epidemiology of *Candida* bloodstream infection means that in vitro testing should include genus- and species-specific susceptibility testing to support clinical decisions.

The use of fluconazole prophylaxis has been associated with the increase in colonization and disease from azole resistant *Candida* strains [4, 5]. It is reported that, in patients with more than 2 weeks azole prophylaxis, over 17% of *Candida* spp. exhibited a reduced susceptibility to fluconazole [6]. Intrinsic low-level and acquired high-level azole resistance of *C. glabrata* has been postulated to have contributed to the emergence of this fungal pathogen in the intensive care unit [6]. As the use of the echinocandins has increased so has selection pressure, and sporadic reports of echinocandin resistance have begun to appear in the literature [7]. The molecular mechanisms of resistance to the echinocandins relate to amino acid substitutions within the FKS1 target gene. At the time of this patient's treatment, the Clinical Laboratory Standards Institute (CLSI) suggested a "susceptible only" breakpoint of < 2 µg/mL for *Candida* spp. for caspofungin, micafungin and anidulafungin [8]. However, infections involving isolates with target alterations in the FKS1 gene did not necessarily show minimum inhibitory concentration (MICs) above this breakpoint [9, 10]. In addition, in vitro susceptibility testing does not take into account the effect of serum protein binding, which may influence the relative clinical efficacy of the echinocandins [10]. Thus, MIC and susceptibility testing are often poor predictors of clinical outcome in *Candida* bloodstream infection [11]. Recently, the CLSI have reset the breakpoints for *Candida* based on pharmacokinetic and pharmacodynamic modeling. Echinocandin breakpoints for *Candida* are now species specific and in the case of *C. glabrata*, different for micafungin than to caspofungin [12]. Similarly, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) have also set drug-specific breakpoints for *Candida* for each of the echinocandin drugs, although due to inter laboratory variation in MIC ranges, the breakpoints for caspofungin against *C. glabrata* have not yet been established by EUCAST [13].

Here we report a case of breakthrough *Candida* blood-

Table 1. Antifungal Agent Sensitivities to Seven *Candida glabrata* Isolates Taken From Case Study Patient

Antifungal agent	Isolate number (date of isolation in 2008)						
	18,776 (20/09)	18,779 (23/09)	18,778 (24/09)	18,777 (29/09)	18,775 (02/10)	18,774 (03/10)	18,773 (04/10)
Flucytosine	SD	SD	SD	SD	SD	SD	SD
Amphotericin	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Fluconazole	8	8	8	8	8	8	8
Itraconazole	1	2	1	2	1	1	2
Voriconazole	0.25	0.25	0.25	0.125	0.125	0.5	0.25
Caspofungin	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Micafungin	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015	≤ 0.015

SD: sensitive by disc test.

stream infection in a 16-year-old male who had previously undergone an emergency laparotomy and had received repeated courses of fluconazole and caspofungin.

Case Report

In July 2008, a 16-year-old male weighing 50 kg was admitted to hospital with a previous history of constipation and a 4-day history of abdominal pain. Vital signs on admission included a respiratory rate of 32 bpm, blood pressure of 111/60 mmHg, and temperature of 38 °C. The patient was clinically dehydrated and peritonitic; a chest X-ray showed free intraperitoneal gas. Emergency laparotomy revealed a well-established perforation of the mid-sigmoid colon and extensive fecal contamination. A Hartmann's procedure was carried out, followed by thorough peritoneal lavage and primary abdominal closure. The patient was subsequently transferred to intensive care. In the post-operative period antibacterial prophylaxis with cefuroxime (750 mg, TDS, days 1 to 6), metronidazole (500 mg, TDS, days 1 to 6), piperacillin-tazobactam (4.5 g, TDS, Days 6 to 12), gentamicin (320 mg, OD, days 7 to 13) and erythromycin (250 mg, TDS, days 7 to 12) was given.

Recovery from surgery was hampered by multiple infectious complications. On day 3, the patient became pyrexial with a temperature of 39.2 °C. *Staphylococcus epidermidis* was cultured from blood cultures. The CVC was replaced on Day 9 from which *Candida tropicalis* was reported on day 12; in view of this, fluconazole 400 mg OD was then started. Despite continued combined anti-microbial (meropenem 1

g, TDS days 13 to 18) and anti-fungal therapy, blood cultures remained positive for S. epidermidis and *C. tropicalis*.

On day 12, the patient also developed a wound infection, and CT scan revealed a pelvic collection. Following dehiscence of the abdominal wound on day 16 which was treated with a VAC dressing, the patient developed a high volume enterocutaneous fistula on day 23 which drained several liters of effluent a day. The CVC was replaced on day 19, and again on day 26, when a Hickman line was introduced instead. The CVC tip culture returned as *C. albicans* positive. On day 35, fluconazole was replaced with caspofungin (70 mg first dose and then 50 mg OD) due to persistent fever and positive *C. tropicalis* blood culture. Two further line changes also followed. On day 46, the patient's fever finally abated and bloods returned without fungal-positive cultures. During caspofungin therapy the patient also received antimicrobial therapy with meropenem (1 g, TDS, days 35 to 46), vancomycin (1 g, BD, days 41 to 45) and gentamicin (240 mg, OD, days 32 to 38).

After a couple of days of being afebrile, the patient respiked a temperature, and blood cultures once again became positive for *S. epidermidis*. The CVC was changed for the sixth time and the patient received gentamicin therapy between days 48 and 51. On day 55, meropenem (1 g, TDS) and vancomycin (1 g, BD) were restarted and given until day 62. On day 60, blood cultures returned positive for *C. glabrata*. Fluconazole 400 mg OD was re-started and the CVC line changed again. Based on sensitivities (Table 1), the fluconazole therapy was replaced with caspofungin on day 66. The ninth CVC was removed and a peripherally inserted central catheter (PICC) was inserted instead. Despite continued ca-

spofungin therapy, the patient's condition did not improve. On day 84, the PICC line was replaced under cefuroxime, caspofungin plus voriconazole cover for 48-hours while micafungin availability was arranged by pharmacy. Taurolidine citrate 4% line lock was used for the PICC. Micafungin 100 mg OD was started on day 86. On day 89, the PICC line had to be removed for non-infective reasons and a Hickman line inserted with continued taurolodine lock. Micafungin was given between days 86 to 101, and the patient had no further episodes of infection. The patient received TPN for the whole of this period.

The seven isolates of *C. glabrata* were tested in-house (fluconazole MIC 8 mg/mL) and by the Mycology Regional Laboratory, Wythenshawe Hospital for their antifungal susceptibility. Azoles were tested using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) method [14], amphotericin B using the Rex method [15] and caspofungin and micafungin using the CLSI M27-A3 method [8] (Table 1).

In summary, between days 11 and 46, the patient developed persistent *Candida* bloodstream infection (9 positive blood cultures) with *C. tropicalis* successfully treated with caspofungin. However, between days 62 and 77, the patient again developed persistent *Candida* bloodstream infection (8 positive blood cultures) this time with *C. glabrata* that did not respond to caspofungin but which responded to micafungin and concomitant lock therapy with taurolidine 4% citrate.

After an in-patient stay in excess of three months, the patient was transferred to a specialist centre. He remained afebrile with the same Hickman line and had no further infectious complications. The patient developed inevitable intestinal failure and remained on home parenteral nutrition. In the following months, he went on to have reconstructive bowel surgery in the form of closure of the abdominal wall defects and resection of small bowel fistulae; the double barreled jejunostomy which was created has since been closed and the patient has been left with a colostomy.

Discussion

Literature reports breakthrough *Candida* bloodstream infection with in vitro-susceptible *Candida* strains during empiric therapy with fluconazole [16]. We believe that this case study represents the first documented European case of successful treatment of breakthrough *C. glabrata* infection with micafungin following unsuccessful treatment with caspofungin. The condition of the patient improved, and fever resolved, after the third Hickman line change and initiation of treatment with micafungin. The therapeutic failure of caspofungin against a then - considered susceptible *C. glabrata* strain is a matter of concern and raises a number of issues.

The relevance of MIC testing for the echinocandins remains unclear [9]. The lack of correlation between elevated

MICs and clinical outcome with other antifungals, namely the azoles, was first reported in the literature in 1995 [17]. In this study 232 isolates were collected during a clinical trial of fluconazole and amphotericin B for the treatment of *Candida* bloodstream infection in non-neutropenic patients. Elevated MICs did not correlate with treatment failure in this study, indeed treatment outcome was successful in four patients despite MICs of > 32 μg/mL. This study group suggested that host factors (such as failure to exchange CVCs) may be more important than MIC in predicting outcome. Uncertain correlation between higher MIC and successful clinical outcome with *C. parapsilosis* has also been reported in the literature [18]. To investigate the relationship between MIC and outcome, a retrospective analysis of isolates from the caspofungin clinical trial database was undertaken that found no correlation between lower MICs and favorable outcome; indeed, patients with higher MICs (> 2 μg/mL) had better outcomes [19]. These studies highlight the difficulty of interpreting antifungal MIC results in the clinical setting. Although Etests have been shown to produce a wider distribution of MICs than either culture or broth microdilution, no one test has been shown to generate results that significantly correlate with success or failure [20].

Guidelines recommend that in the presence of elevated MICs to the echinocandins; organism identification and susceptibility testing should be confirmed using a CLSI reference dilution method [21]. The CLSI has now recommended species specific echinocandin breakpoints for *Candida* species. For *C. glabrata*, the susceptible breakpoint for micafungin is lower (0.012 μg/mL) than for caspofungin or anidulafungin (0.06 mg/mL). Looking back at the susceptibilities retrospectively, the *C. glabrata* strain in this patient was resistant (0.5 μg/mL) to caspofungin but was susceptible (≤ 0.015 μg/mL) to micafungin [12]. Pharmacokinetic/pharmacodynamic modeling techniques have provided more accurate information for current and future decision-support analysis.

The points raised in this discussion highlight how the choice of a suitable anti-fungal drug is of paramount importance in the treatment of patients with *Candida* bloodstream infections. Although amphotericin B, based on its broad spectrum of activity against *Candida* spp., could be argued to have been an option to consider in this patient, both the Infections Diseases Society of America (IDSA) and European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the management of candidiasis [2, 22] recommend an echinocandin in preference over amphotericin B for non-neutropenic patients with *Candida* bloodstream infections, due to concerns of amphotericin B's toxicity. The high degree of well-documented cross-resistance within the azole class [2, 22] would have also limited the usefulness of alternative azole agents such as voriconazole for this particular patient following treatment failure with fluconazole.

Other issues in the management of patients with *Candida* bloodstream infection include host factors, the role of biofilms and the use of line locks. This case of a patient with many of the known risk factors for *Candida* bloodstream infection, including TPN, abdominal surgery and the use of broad spectrum antibiotics, clearly illustrates the difficulty of managing such patients in clinical practice. Interestingly, in this case there were no further breakthrough *Candida* bloodstream infections after the Taurolock™ (TauroPharm GmbH, Germany) was introduced as a line lock and the switch to micafungin as the antifungal agent. Micafungin, has lower MICs than other members of the class against *C. glabrata* (Table 1), which despite the lack of robust evidence for a relationship between MIC and outcome, may have been a contributing factor in the resolution of the multiple *Candida* bloodstream infections in this patient. Further clinical studies are needed to assess the relevance of MIC to outcome and the influence of other management strategies such as lock therapy, in the complex management of patients with multiple co-morbidities and invasive fungal infections.

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Conflicts of Interest

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Declaration

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