Treatment of *Candida famata* bloodstream infections: case series and review of the literature

Nicholas D. Beyda$^{1,2}$, Shen Hui Chuang$^3$, M. Jahangir Alam$^1$, Dhara N. Shah$^{1,2}$, Tat Ming Ng$^3$, Laurie McCaskey$^2$ and Kevin W. Garey$^{1,2}$*

$^1$University of Houston College of Pharmacy, 1441 Moursund Street, Houston, TX 77030, USA; $^2$St Luke’s Episcopal Hospital, 6720 Bertner Avenue, Houston, TX 77030, USA; $^3$Department of Pharmacy, National University of Singapore, 18 Science Drive 4, Singapore 117543, Republic of Singapore

*Corresponding author. University of Houston College of Pharmacy, 1441 Moursund Street, Houston, TX 77030, USA. Tel: +713-795-8386; Fax: +713-795-8383; Email: kgarey@uh.edu

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**Objectives:** *Candida famata* (also known as *Debaryomyces hansenii* and *Torulopsis candida*) is a commensal yeast found in cheese, dairy products and the environment. *C. famata* accounts for 0.2%–2% of invasive candidiasis. The purpose of this study was to provide an overview of the treatment of *C. famata* bloodstream infections.

**Methods:** The clinical course of two hospitalized patients who developed *C. famata* fungaemia within 2 weeks of each other was summarized along with available data regarding in vitro susceptibility patterns, genotyping and clinical outcomes of these cases compared with the published literature.

**Results and conclusions:** *C. famata* appears to exhibit reduced susceptibility to echinocandins and azoles, particularly in the setting of prior antifungal exposure. The removal of indwelling central venous catheters and prompt initiation of therapy with liposomal amphotericin B is recommended for successful treatment of *C. famata* fungaemia, particularly in immunocompromised patients. These cases also help provide justification for routine antifungal susceptibility testing in patients with candidaemia to guide optimal antifungal therapy.

**Keywords:** *Candida* bloodstream infections, susceptibility testing, echinocandins, strain typing, literature review

**Introduction**

*Candida famata* (also known as *Debaryomyces hansenii* and *Torulopsis candida*) is a commensal yeast found in cheese, dairy products and the environment. It has been described in human infections, including catheter-related bloodstream infections, peritonitis, acute zonal occult retinopathy and mediastinitis. It is a rare cause of candidiasis, accounting for only 0.2%–2% of isolates collected from antifungal surveillance studies. Elevated MICs of antifungal agents have been described and are a concern when treating invasive candidiasis due to *C. famata*. Here we describe the clinical course of two hospitalized patients who developed *C. famata* fungaemia within 2 weeks of each other and summarize available data regarding in vitro susceptibility patterns, genotyping and clinical outcomes of these cases compared with the published literature.

**Methods**

Patients were identified at a university-affiliated tertiary care hospital in the Texas Medical Center, Houston, TX, USA, during 2012 as part of an ongoing, surveillance study of patients with candidaemia. In this study approved by the institutional review board, *Candida* isolates are collected from the clinical microbiology laboratory and clinical information is collected from the medical chart. A waiver of informed consent was approved for this study. The patient’s clinical course was described briefly and the isolates were collected for further microbiological testing. All isolates were initially identified to the species level by the clinical microbiology laboratory using Vitek II yeast cards (bioMérieux, Marcy l’Etoile, France) and API 20c AUX (bioMérieux). Antifungal susceptibility testing was also performed by the clinical microbiology laboratory using semi-automated broth microdilution (Sensititre) according to CLSI guidelines as previously described.

**Confirmation of *C. famata***

**Results and conclusions:** *C. famata* appears to exhibit reduced susceptibility to echinocandins and azoles, particularly in the setting of prior antifungal exposure. The removal of indwelling central venous catheters and prompt initiation of therapy with liposomal amphotericin B is recommended for successful treatment of *C. famata* fungaemia, particularly in immunocompromised patients. These cases also help provide justification for routine antifungal susceptibility testing in patients with candidaemia to guide optimal antifungal therapy.

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DiversiLab Candido Fingerprinting Kit (bioMérieux). Amplification products were separated by microfluidic electrophoresis using a DNA Lab Chip and an Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA). Data were analysed using the web-based DiversiLab software (v3.4). Results were presented as a dendrogram using the Pearson correlation similarity matrix for each DNA sample. Isolates were considered indistinguishable (>97% similarity and 0 band differences), similar (>95% similarity and <2 band differences) or different (<95% similarity or >3 band differences). Finally, a systematic review of the literature was performed using the search engine PubMed and the search term ‘Candida famata’.

Results

Case presentations

Case 1

An elderly (>60 years old) Caucasian male was admitted to the hospital with chief complaints of fatigue, weight loss and bleeding gums for 1 month. His past medical history was significant for hypertension and psoriasis. Initial blood counts showed a leukaemic process with a white count of 14 500 cells/mL with 42% blastocytes. An emergent bone marrow biopsy revealed acute myelogenous leukaemia with tri-lineage hyperplasia and 74% blastocytes. On hospital day 4, he underwent induction chemotherapy with idarubicin and cytarabine and was started on 200 mg of posaconazole orally three times daily. He subsequently developed neutropenic fever and blood cultures grew Pseudomonas aeruginosa, which was treated with piperacillin/tazobactam and resolved. A repeat bone marrow biopsy was done on hospital day 33, which showed 5%-10% blastocytes and minimal disease. His second cycle of chemotherapy was started on hospital day 43 with cytarabine, etoposide and mitoxantrone. Five days later (hospital day 48), posaconazole was discontinued and 200 mg of voriconazole orally twice daily was started. On hospital day 61, the patient continued to be pancytopenic and again developed neutropenic fever; 100 mg of micafungin intravenously daily was added empirically. A left lower lobe bronchiolar lavage was done on hospital day 66 due to pleural effusion, which subsequently grew Candida guilliermondii. Nine days later (hospital day 75) he developed another episode of neutropenic fever and blood cultures were obtained. Two days later, the aerobic blood culture obtained from the right peripherally inserted central catheter (PICC) turned positive with yeast. At this time (hospital day 77), the right PICC line was removed and a new one was placed on the left arm, voriconazole was discontinued and 340 mg of liposomal amphotericin B intravenously daily was started. On hospital day 81, micafungin was discontinued after the isolate was identified as C. famata and antifungal susceptibility results were reported (Tables 1 and 2). Repeat blood cultures obtained 1 week later were negative.

Case 2

An elderly (>80 years old) African American male was admitted to the hospital due to increasing abdominal pain since last admission with a white blood cell count of 31 800 cells/mL. He had several recent medical admissions for right lower lobe pneumonia that was treated with levofloxacin and abdominal distension with megacolon requiring total parenteral nutrition and rectal tube placement. His past medical history was significant for hypertension, chronic kidney disease, benign prostate hyperplasia, gout and chronic obstructive pulmonary disease. At this admission, he was diagnosed with aspiration pneumonia and was started on 1 g of cefepime intravenously daily. He subsequently developed respiratory failure requiring mechanical ventilation. He also developed a small bowel obstruction and acute on chronic kidney injury requiring haemodialysis. In addition, he completed 2 weeks of intravenous fluconazole for C. albicans candiduria and underwent cystoscopy for haematuria. On hospital day 34, he became febrile, with a temperature of 103.1°F, and 100 mg of micafungin intravenously daily and 250 mg of doripenem intravenously twice daily were started and a single intravenous dose of 1 g of vancomycin was given empirically. Blood cultures were obtained on two separate occasions (hospital days 34 and 36) and all returned positive for yeast within 2 days. On hospital day 37, the patient’s right internal jugular vein tunnelled haemodialysis catheter and left arm PICC line were removed. On hospital day 40, the yeast from the positive blood cultures was identified as C. famata and antifungal susceptibility results were reported (Tables 1 and 2). The PICC line tip was also reported to be positive with

Table 1. Antifungal susceptibilities of C. famata

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Case 1, index isolate (MIC (mg/L))</th>
<th>Case 2, index isolate (MIC (mg/L))</th>
<th>Repeat isolate (MIC (mg/L))</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FC</td>
<td>≤0.06</td>
<td>≤0.06</td>
<td>≤0.06</td>
</tr>
<tr>
<td>AmB</td>
<td>≤0.12</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>ANI</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CAS</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>MCF</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>FLU</td>
<td>128</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>ITR</td>
<td>16</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>POS</td>
<td>2</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>VRC</td>
<td>4</td>
<td>0.12</td>
<td>0.12</td>
</tr>
</tbody>
</table>

5-FC, 5-flucytosine; AmB, amphotericin B; ANI, anidulafungin; CAS, caspofungin; MCF, micafungin; FLU, fluconazole; ITR, itraconazole; POS, posaconazole; VRC, voriconazole.

Table 2. Identification of C. famata in index cases by commercial biochemical identification

<table>
<thead>
<tr>
<th>Case</th>
<th>Vitek II species (% ID)</th>
<th>API 20c AUX species (% ID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Candida famata or Candida guilliermondii (low discrimination)</td>
<td>Candida famata (85.8%) or Candida guilliermondii (14%) or Candida lusitaniae (0.1%)</td>
</tr>
<tr>
<td>2</td>
<td>Candida famata (95%)</td>
<td>Candida famata (39.6%) or Candida guilliermondii (60.3%)</td>
</tr>
</tbody>
</table>

Vitek II bionumbers: 6506555275311371 (Case 1) and 4546555675313371 (Case 2). API 20c AUX accession numbers: 6316333 (Case 1) and 6756373 (Case 2). %ID, probability of correct identification.

 blender
>100 colonies of *C. famata* on direct plating on hospital day 40. Repeat blood cultures were obtained at this time and were reported negative at 5 days.

**Molecular analysis**

The index isolates from Patient 1 and Patient 2 and the subsequent blood isolate from Patient 2 obtained 2 days later were available for PCR analysis and genotyping. All three isolates were confirmed to be *C. famata* by PCR. Genotyping results indicated that the isolate from Patient 1 was a different strain than those found in Patient 2, with a similarity of 77% and numerous banding differences (Figure 1). The two isolates from Patient 2 had a high degree of similarity (97%) and indistinguishable banding patterns, indicating they were the same strain.

**Review of the literature for *C. famata***

A PUBMED search was conducted using the search term ‘*Candida famata*’. No limits were set. Three case reports and one case series of *C. famata* fungaemia were identified (Table 3). All reported cases of *C. famata* fungaemia occurred in immunocompromised hosts or burn patients. The majority of the cases were treated with liposomal amphotericin B (80%). Two patients received fluconazole monotherapy and one patient received liposomal amphotericin B in combination with caspofungin followed by voriconazole. The treatment duration ranged from 14 to 32.5 days. Both of our cases initially received micafungin with one of two patients receiving definitive therapy with liposomal amphotericin B alone. All studies except Wagner et al. documented the removal of central venous catheters (CVCs) when fungaemia was diagnosed. A majority of the cases received broad-spectrum antibiotics (carbapenems, ciprofloxacin, teicoplanin) prior to the onset of *C. famata* candidaemia. Among the 10 cases reported, only one case received prophylactic low-dose liposomal amphotericin B. None of the cases reviewed received azole or echinocandin antifungals prior to the development of *C. famata* fungaemia. Overall, the mortality rate observed in 10 reported cases of *C. famata* fungaemia was low (10% mortality rate). In the one case where the patient did not survive, the cause of death was multifactorial, as the patient had a positive galactomannan antigen and radiographic evidence suggesting disseminated Aspergillus infection, and *Scopulariopsis brevicaulis* was cultured from bronchial secretions shortly before death. The cause of death was therefore multifactorial and not solely attributable to *C. famata* fungaemia. Only one case report included antifungal susceptibility results. The *C. famata* isolate was documented to have reduced susceptibility to fluconazole (MIC 32 mg/L) and amphotericin B (MIC 3 mg/L). As the patient was an allogenic stem cell transplant recipient for severe aplastic anaemia, the reduced susceptibility to fluconazole and amphotericin B may have been due to prior antifungal exposure, although this was not documented for this case.

A total of eight articles describing in vitro susceptibility of *C. famata* isolates to various antifungal agents were identified (Table 4). Out of all the *C. famata* isolates combined from the various studies, isolates were most susceptible to amphotericin B. *C. famata* isolates with elevated MICs of fluconazole and itraconazole were observed in these surveys. Of the four studies that conducted echinocandin susceptibility testing for *C. famata*, one study reported susceptibility results for all three echinocandins, two studies reported caspofungin susceptibility only and one reported anidulafungin susceptibility only. In three of the four studies, isolates with elevated echinocandin MICs were noted.

**Discussion**

Predisposing risk factors for *C. famata* fungaemia identified from published case reports and case series include the presence of a CVC, prior exposure to antibiotics and antifungals, immunocompromised states and disruptions of skin flora. In our cases, both patients had many of the same risk factors present prior to the development of *C. famata* fungaemia. In particular, Patient 1 was severely immunocompromised and pancytopenic for a significant amount of time, had a CVC in place and had been exposed to broad-spectrum antibacterial and antifungal agents. Patient 2 also had similar risk factors for *C. famata* fungaemia, including the presence of a CVC and exposure to broad-spectrum antibiotics and antifungals. However, this patient was not immunocompromised, making this the first reported case of *C. famata* fungaemia in a non-neutropenic, non-burn patient.

Data from a limited number of studies evaluating the antifungal susceptibility profile of *C. famata* indicate that this species may have reduced susceptibility to commonly used antifungals.
such as fluconazole and the echinocandins. The isolate from Patient 1 displayed high-level resistance to all the azoles, which may have been due to the extensive posaconazole and voriconazole pre-exposure. The isolates from Patient 2, however, had relatively low azole MICs despite previous exposure to fluconazole for 2 weeks. Isolates from both patients displayed elevated MICs of all three echinocandins relative to what is typically observed for other Candida spp. Several studies have shown that C. famata may have reduced echinocandin susceptibility compared with other Candida spp. Similarly, both C. parapsilosis and C. guilliermondii also display reduced echinocandin susceptibility compared with other Candida spp., which has been linked to intrinsic mutations within the highly conserved FKS1 gene. Whether or not similar mutations are found in C. famata has not been reported.

Phenotypic differentiation of C. famata and C. guilliermondii is extremely difficult as these two species share many of the same biochemical and morphological characteristics. This difficulty was illustrated nicely in the current cases in which both the Vitek II and API 20c AUX results were necessary to provide the most likely species identification. In a study by Desnos-Ollivier et al., only 3 of 26 isolates initially identified as being C. famata by phenotypic methods were confirmed to be C. famata by sequencing the ITS and D1/D2 regions of the rRNA gene. Based on these results, it is possible that previously published case reports of C. famata fungaemia may have been misidentified, as further confirmation using genetic sequencing was not performed. Due to the possibility of misidentification using phenotypic techniques, we confirmed the results of Vitek II and API 20c AUX using a multiplex PCR technique. Isolation of both C. famata from the blood culture and C. guilliermondii from the respiratory specimen from the first patient in this report was an interesting observation. Unfortunately, the respiratory isolate from Patient 1 was unavailable for testing to confirm speciation.

As there is a paucity of data regarding antifungal susceptibility and clinical outcomes of C. famata fungaemia, a validated treatment recommendation is difficult to discern. However, based on the in vitro and clinical evidence gathered from the limited number of published studies and our own centre's experience in treating C. famata fungaemia, prompt removal of indwelling CVCs and antifungal susceptibility testing is highly recommended. As in vitro studies have documented good susceptibility to amphotericin B, but reduced susceptibility to both fluconazole and echinocandins, treatment with amphotericin B should be considered until susceptibility is confirmed.

Conclusions

There is a paucity of data on clinical outcomes and the in vitro susceptibilities of C. famata to antifungal agents. C. famata appears to exhibit reduced susceptibility to echinocandins and azoles, particularly in the setting of prior antifungal exposure. The removal of indwelling CVCs and prompt initiation of therapy with liposomal amphotericin B is recommended for successful treatment of C. famata fungaemia, particularly in immunocompromised patients. The cases described in this report also help provide justification for routine antifungal susceptibility testing in patients with candidaemia to guide optimal antifungal therapy.
Funding
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Transparency declarations
K. W. G. has received research support from Astellas Pharma Global Development, Inc. All other authors: none to declare.

References
7 Kawakami S, Ono Y, Miyazawa Y et al. [Survey of fungemia cases during the past seventeen years at Teikyo University Hospital]. Kansenshogaku Zasshi 1998; 72: 105–13.

Table 4. In vitro susceptibilities of C. famata isolates to antifungal agents

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of isolatesa</th>
<th>Site of specimens</th>
<th>MIC50 (mg/L)</th>
<th>azoles</th>
<th>AmB</th>
<th>echinocandins</th>
<th>5-FC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>15/98</td>
<td>blood, urine, GI, sputum</td>
<td>FLU: 64</td>
<td>0.125</td>
<td>ND</td>
<td>&lt;1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>KET: 0.25</td>
<td></td>
<td></td>
<td>POS: &lt;1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ITR: 0.25</td>
<td></td>
<td></td>
<td>VRC: &lt;1</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>10/314</td>
<td>blood</td>
<td>FLU: 16</td>
<td>&lt;1</td>
<td>ND</td>
<td>0.25–64 (range)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ITR: 1</td>
<td></td>
<td></td>
<td>POS: &lt;1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VRC: &lt;1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>9/3959</td>
<td>blood, CSF, pleural or peritoneal fluid</td>
<td>FLU: 2</td>
<td>ND</td>
<td>CAS: 4</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ITR: 0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>10/460</td>
<td>blood, vagina, urine, oropharynx</td>
<td>FLU: 16</td>
<td>ND</td>
<td>ANI: 8</td>
<td>ND</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>ITR: 1</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2004</td>
<td>18/643</td>
<td>blood</td>
<td>FLU: 0.5</td>
<td>&lt;0.03</td>
<td>CAS: &lt;0.03</td>
<td>0.5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>KET: 0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VRC: &lt;0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>2/114</td>
<td>blood, urine, sputum</td>
<td>FLU: 0.5</td>
<td>2</td>
<td>ND</td>
<td>0.25</td>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VRC: &lt;0.03</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>2008</td>
<td>24/5346</td>
<td>blood</td>
<td>FLU: ≤8</td>
<td>≤1</td>
<td>ND</td>
<td>≤4</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>4/38</td>
<td>blood</td>
<td>FLU: ≤8</td>
<td>≤1</td>
<td>ND</td>
<td>≤4</td>
<td></td>
</tr>
</tbody>
</table>

AmB, amphotericin B; 5-FC, 5-flucytosine; FLU, fluconazole; KET, ketoconazole; ITR, itraconazole; POS, posaconazole; VRC, voriconazole; RAV, ravuconazole; CAS, caspofungin; MCF, micafungin; ANI, anidulafungin; GI, gastrointestinal; ND, not determined.
aNumber of C. famata isolates out of total number of Candida spp. isolates.
bMIC50 reported.


Ozcelik B, Kaynak F, Cesur S et al. In vitro activities of voriconazole as a triazole derivative and caspofungin as an echinocandin were compared with those of some antifungal agents against Candida species isolated from clinical specimens. Jpn J Infect Dis 2007; 60: 302–4.


