Candida lusitaniae Infections in the Era of Fluconazole Availability

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Amphotericin B resistance among isolates of Candida lusitaniae has distinguished it among Candida species. Because no comprehensive review has been published recently, we provide a case report and a literature review of C. lusitaniae infection to update and better characterize the illness in the era ofazole availability and standardized methodologies for antifungal susceptibility testing. C. lusitaniae infection in the 55 cases surveyed in this review occurred in relatively young patients (median age, 44 years). Fungemia was found in 80% of patients. Other infection syndromes, including peritonitis, meningitis, and urinary tract infection, were much less common. Three-fourths of the patients had serious underlying medical conditions. Despite the presence of fungemia and predisposing comorbidities, death due to C. lusitaniae infection was uncommon among treated patients (5.00%). Moreover, in vitro susceptibility testing results for amphotericin B did not appear to predict patient outcome in this survey.

Candida lusitaniae is an uncommon pathogen and is noteworthy because some isolates are resistant to amphotericin B (AmB) [1–3]. No comprehensive literature review of C. lusitaniae infection has been published since 1990, when fluconazole, an azole antifungal drug with in vitro activity against C. lusitaniae, became available. We describe a case and review the literature from 1990–2001 to better characterize C. lusitaniae infections and to examine the impact of currently available therapies on patient outcome.

CASE REPORT

A 77-year-old woman with end-stage renal disease had fever documented during a routine hemodialysis session. Two sets of blood samples were drawn for culture; the cultures were positive for yeast. The patient was initially treated with oral fluconazole. Subsequently, her hemodialysis catheter access site became erythematous, and the access catheter was removed. Fluconazole, 400 mg iv q48h, was administered. Ophthalmologic evaluation showed no evidence of infection. Transthoracic echocardiography was performed and revealed a lesion on the patient’s mitral valve. Transesophageal echocardiography was performed and did not demonstrate valvular abnormalities or mass lesions. An indium-labeled leukocyte scan was performed and the results were negative. Initial blood samples drawn at the hemodialysis clinic grew C. lusitaniae. Culture of the access catheter tip showed no growth. The isolate was sent to a reference laboratory for susceptibility testing according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines [4], and results indicated that the isolate was susceptible to fluconazole, AmB, itraconazole, and 5-fluorocytosine. The patient’s mental status improved, and subsequent blood cultures showed no growth. She was discharged home and completed a 19-day course of fluconazole therapy. Four months after completion of therapy, the patient had experienced no recurrence of infection, but as a result of declining...
Six patients were children (age, male; 15 (40.5%) were female. The mean and median ages were 50 years; age range, 18–79 years). In vitro studies of C. lusitaniae isolates that contained no clinical information were excluded. Fifty-five cases are included in this review; 54 cases were reported during 1990–2001 [5–30]. Because specific clinical information was not available for every case, the denominator was <55 in most of our analyses.

**Sex and age.** Twenty-two (59.5%) of 37 patients were male; 15 (40.5%) were female. The mean and median ages were 41.8 years and 44 years, with an age range of 8 days to 79 years. Six patients were children (age, <18 years; mean age, 2.57 years; age range, 8 days to 6 years), and 29 were adults (mean age, 50 years; age range, 18–79 years).

**Infection syndrome.** There were 30 patients with deep-seated infections for whom treatment and outcome were described (table 1). These included patients with fungemia, meningitis, peritonitis, endocarditis, chorioamnionitis, osteomyelitis, bursitis, and abdominal abscess. Fungemia was the most common type of C. lusitaniae infection, occurring in 44 (80%) of 55 cases. In 9 cases of fungemia (16.4% of the C. lusitaniae infections), a primary infection focus was identified. Peritonitis (4 [7.3%] of 55 cases), meningitis (3 [5.5%] of 55), urinary tract infection (3 [5.5%] of 55), and vulvovaginitis (2 [3.6%] of 55) were much less frequently described. One case (1.8%) each was reported of chorioamnionitis, olecranon bursitis, infective endocarditis, abdominal abscess, cutaneous infection, and infection of a left ventricular assist device, and C. lusitaniae was isolated from the kidney and pancreas of 1 additional patient at autopsy.

**Underlying conditions.** For 41 (74.6%) of 55 patients, serious underlying medical conditions before the development of C. lusitaniae infection were described. Twenty-nine patients (52.7%) had malignancy, of whom 17 had leukemia or lymphoma, 10 had solid tumors, and 2 had unspecified malignancies. Fourteen patients had received chemotherapy, and 19 patients were neutropenic at the time of infection. Nine patients were receiving long-term corticosteroid therapy, and 15 patients had recently received broad-spectrum antibiotics. Four patients had undergone bone marrow transplantation. Fifteen patients had a central venous catheter in place at the time of infection, and 3 patients had a ventriculoperitoneal shunt. Two patients were undergoing continuous ambulatory peritoneal dialysis and 1 patient was undergoing hemodialysis. Two patients were premature infants.

**Cultures.** For 44 (95.7%) of cases for which blood culture results were reported, cultures grew C. lusitaniae. Cultures of central venous catheters were reported in 12 cases, 5 (41.7%) of which were positive for C. lusitaniae. Other sites for which culture results were positive were as follows: urine (4 cases); peritoneal fluid (3); vagina (2); CSF (2); bursa fluid (1); skin (1); pancreatic and renal tissue obtained postmortem (1); continuous ambulatory peritoneal dialysis catheter (1); and left-ventricular assist device (1). For the patient with chorioamnionitis, positive cultures of amniotic fluid and placental and fetal tissue were positive for C. lusitaniae.

**Susceptibilities.** Antifungal susceptibilities were reported in 23 cases. NCCLS guidelines [4] for MIC breakpoints were used to determine susceptibility to fluconazole, itraconazole, and 5-fluorocytosine in 8 cases [21, 29, 30]. Isolates were considered susceptible to AmB if the MIC was <2 μg/mL. Five (21.7%) of 23 isolates were resistant to AmB. One isolate was initially susceptible to fluconazole and itraconazole but had developed resistance when susceptibility testing was repeated. For 1 isolate, fluconazole was reported to be “fungistatic.” All 8 isolates tested for resistance to 5-fluorocytosine were found to be susceptible.

**Treatment.** Thirty-two of 34 patients received antifungal therapy; the 2 remaining patients died before the results of cultures for C. lusitaniae were available and did not receive therapy with antifungal agents. Eight of the 32 patients were given >1 agent. AmB and fluconazole were the most commonly administered agents (16 of 32 cases each). Drugs used less often included 5-fluorocytosine (6 cases), ketoconazole (3), itraconazole (1), and miconazole (1). Two patients with vulvovaginitis were topically treated with terconazole cream.

**Outcome.** Outcome was reported for 34 patients. Three patients with C. lusitaniae infection (8.8%) died, 2 of whom received no antifungal therapy. The remaining 31 patients either survived (25 patients [73.5%]), died from other causes (4 patients [11.8%]), or were reported to have infections that failed to respond to treatment (2 patients [5.9%]) with no other outcome information provided.

Survival among patients with fungemia as an infection syndrome was high; of patients who had fungemia and were treated, 95% (19 of 20) survived their infection. For 2 of these patients, death occurred after resolution of infection and was due to noninfectious causes. There were too few cases of other infection syndromes to draw conclusions about outcome.

**DISCUSSION**

A review of C. lusitaniae infections is in order for 3 critical reasons. First, the last comprehensive review of these infections was published in 1987 [2] and included a limited number of cases that had been treated during 1979–1986. Second, fluconazole became available in 1990 and has been used to successfully treat C. lusitaniae infection. Third, antifungal susceptibility test-
Table 1. Clinical and microbiologic features of 30 cases of deep-seated *Candida lusitaniae* infection.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Patient age, sex</th>
<th>Syndrome</th>
<th>Predisposing factors</th>
<th>Blood</th>
<th>Other</th>
<th>MICs for isolate, μg/mL</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [5]</td>
<td>79 y, M</td>
<td>Peritonitis</td>
<td>ESRD, CVL, CAPD, abx</td>
<td>NA</td>
<td>CVL, +; peritoneal fluid, +</td>
<td>NA</td>
<td>AmB NA NA NA NA 5-FC Ket, Mic, cath removed</td>
<td></td>
</tr>
<tr>
<td>2 [6]</td>
<td>14 d, M</td>
<td>Fungemia, UTI</td>
<td>Primy, CVL</td>
<td>+</td>
<td>CVL, +; urine, +</td>
<td>2.0</td>
<td>NA 0.12 NA &lt;0.3 AmB, 5-FC Ket</td>
<td></td>
</tr>
<tr>
<td>3 [8]</td>
<td>35 y, M</td>
<td>Meningitis</td>
<td>Abx</td>
<td>NA</td>
<td>CSF, +</td>
<td>S</td>
<td>NA S NA NA None</td>
<td></td>
</tr>
<tr>
<td>4 [9]</td>
<td>72 y, F</td>
<td>Fungemia</td>
<td>LL, chem, neut, CVL</td>
<td>+</td>
<td>CVL, −</td>
<td>S</td>
<td>NA S NA NA AmB, 5-FC DOC</td>
<td></td>
</tr>
<tr>
<td>5 [11]</td>
<td>8 d, M</td>
<td>Fungemia, osteomyelitis</td>
<td>Primy</td>
<td>+</td>
<td>NA</td>
<td>&lt;0.14 2.5 &lt;10.09 0.07 0.1 AmB, Flu, 5-FC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 [14]</td>
<td>42 y, F</td>
<td>Fungemia</td>
<td>LL, CVL, axb, ster</td>
<td>+</td>
<td>CVL, +</td>
<td>NA NA NA NA Flu, cath removed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 [15]</td>
<td>18 y, F</td>
<td>Fungemia</td>
<td>LL, neut, BMT, chem, ster, XRT, CVL, axb</td>
<td>+</td>
<td>CVL, −</td>
<td>2</td>
<td>0.25 0.03 AmB</td>
<td></td>
</tr>
<tr>
<td>8 [15]</td>
<td>71 y, M</td>
<td>Fungemia, peritonitis</td>
<td>Chem, neut, CVL, axb, LL</td>
<td>+ Peritoneal fluid, +; urine, +; CVL, −</td>
<td>0.5 32</td>
<td>NA 0.25 NA AmB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 [15]</td>
<td>67 y, M</td>
<td>Fungemia, UTI</td>
<td>ST, chem, CVL</td>
<td>+</td>
<td>Urine, +; CVL, −</td>
<td>0.25</td>
<td>2 NA 0.125 NA Flu</td>
<td></td>
</tr>
<tr>
<td>10 [15]</td>
<td>32 y, M</td>
<td>Fungemia</td>
<td>AIDS, neut, CVL, abx</td>
<td>+</td>
<td>CVL, −</td>
<td>NA NA NA NA AmB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 [15]</td>
<td>4 mo, M</td>
<td>Fungemia</td>
<td>CVL, cardiac surgery</td>
<td>+</td>
<td>CVL, +</td>
<td>1 1 0.015 AmB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 [16]</td>
<td>32 y, F</td>
<td>Chorioamnionitis</td>
<td>LL, BMT</td>
<td>+</td>
<td>Amniotic fluid, +; placental tissue, +; fetall tissue, +</td>
<td>1 NA NA AmB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 [17]</td>
<td>59 y, F</td>
<td>Bursitis</td>
<td>SLE, ster</td>
<td>−</td>
<td>Bursa fluid, +</td>
<td>0.25</td>
<td>2 NA 0.125 NA Flu</td>
<td></td>
</tr>
<tr>
<td>14 [18]</td>
<td>60 y, M</td>
<td>Peritonitis</td>
<td>ESRD, CAPD</td>
<td>NA</td>
<td>Peritoneal fluid, +</td>
<td>NA NA NA NA NA Ket</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 [19]</td>
<td>6 y, M</td>
<td>Meningitis</td>
<td>ST, abx, VPS</td>
<td>NA</td>
<td>CSF, +</td>
<td>NA NA NA NA Flu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 [20]</td>
<td>20 y, F</td>
<td>Fungemia</td>
<td>LL, CVL, abx, neut</td>
<td>+</td>
<td>NA</td>
<td>NA NA NA NA AmB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17 [20]</td>
<td>20 y, F</td>
<td>Fungemia</td>
<td>CVL, abx, neut, LL</td>
<td>+</td>
<td>NA</td>
<td>NA NA NA NA Flu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 [20]</td>
<td>20 y, M</td>
<td>Fungemia</td>
<td>LL, abx, CVL, neut</td>
<td>+</td>
<td>NA</td>
<td>NA NA NA NA Flu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 [21]</td>
<td>41 y, F</td>
<td>Endocarditis</td>
<td>PAV</td>
<td>+</td>
<td>NA</td>
<td>&lt;0.5 0.4 &lt;0.2 3.1 AmB, 5-FC, Flu, valve replaced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 [22]</td>
<td>22 y, NA</td>
<td>Fungemia</td>
<td>LL, CVL, abx, neut</td>
<td>+</td>
<td>NA</td>
<td>NA NA NA NA AmB, catheter removed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 [22]</td>
<td>29 y, M</td>
<td>Fungemia</td>
<td>ST, CVL, abx, neut</td>
<td>+</td>
<td>NA</td>
<td>NA NA NA NA Flu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22 [22]</td>
<td>3 y, NA</td>
<td>Fungemia, meningitis</td>
<td>ST, CVL, abx, VPS</td>
<td>+</td>
<td>NA</td>
<td>2 1 NA NA Flu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23 [28]</td>
<td>52 y, F</td>
<td>Fungemia, abd. abscess</td>
<td>CVL, abx</td>
<td>+</td>
<td>CVL, +</td>
<td>0.38</td>
<td>NA NA NA NA Flu, CVL removed</td>
<td></td>
</tr>
<tr>
<td>24 [29]</td>
<td>59 y, F</td>
<td>Fungemia</td>
<td>LL, neut, chem</td>
<td>+</td>
<td>NA</td>
<td>0.25 0.25 NA 0.125 NA None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 [29]</td>
<td>70 y, M</td>
<td>Fungemia</td>
<td>ST, neut, chem, ster</td>
<td>+</td>
<td>NA</td>
<td>1 1 0.015 NA Flu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 [29]</td>
<td>28 y, F</td>
<td>Fungemia</td>
<td>LL, chem, neut</td>
<td>+</td>
<td>NA</td>
<td>0.5 0.25 NA 0.125 AmB, Flu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27 [29]</td>
<td>20 y, F</td>
<td>Fungemia</td>
<td>LL, BMT, neut, chem, ster</td>
<td>+</td>
<td>NA</td>
<td>0.25 &gt;1 0.25 &gt;64 NA 0.125 &gt;64 AmB, Flu, Ket</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 [29]</td>
<td>47 y, F</td>
<td>Fungemia</td>
<td>ST, BMT, neut, chem</td>
<td>+</td>
<td>NA</td>
<td>0.5 16 NA 0.125 AmB, Flu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29 [30]</td>
<td>6 y, NA</td>
<td>Fungemia</td>
<td>ST, VPS</td>
<td>+</td>
<td>VPS, +</td>
<td>2 1 NA NA Flu, VPS removed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 (PR)</td>
<td>77 y, F</td>
<td>Fungemia</td>
<td>ESRD, CVL</td>
<td>+</td>
<td>CVL, −</td>
<td>0.13 0.25 &lt;0.25 &lt;0.015 NA Flu</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Abd., abdominal; abx, antibiotic therapy; AmB, amphotericin B; BMT, bone marrow transplant; CAPD, chronic ambulatory peritoneal dialysis; chem, chemotherapy; CVL, central venous line; d, days; D, died; DOC, died from other cause; ESRD, end-stage renal disease; Flu, fluconazole; Itr, itraconazole; Ket, ketoconazole; LL, leukemia/lymphoma; Mic, miconazole; mo, months; NA, not available; neut, neutropenia; PAV, prosthetic aortic valve; PR, present report; primy, premature infant; ref., reference; S, survived; SLE, systemic lupus erythematosus; ST, solid tumor; ster, corticosteroid therapy; TF, treatment failure; UTI, urinary tract infection; VPS, ventriculoperitoneal shunt; XRT, radiation therapy; y, years; 5-FC, 5-fluorocytosine; +, positive; −, negative.

* Reported as fungistatic.
ing methodologies were approved in 1997 [4] for use with isolates of Candida species.

The previous review [2], which included only 9 cases of C. lusitaniae infection, could not fully characterize the illness. In contrast, 55 cases are included in the present survey. One-half of the patients were <45 years old. Fungemia was the most common infection syndrome and was described in >80% of patients. Peritonitis, meningitis, urinary tract infection, and other infection syndromes were infrequently seen. Malignancy and its associated treatment were present in almost one-half of the cases. AmB and fluconazole were the antifungals most commonly used for therapy. Despite the fact that C. lusitaniae infection occurred in immunocompromised patients who often had a number of comorbidities, and despite the fact that fungemia was documented in 96% of patients for whom blood culture results were recorded, death due to fungal infection was infrequent. Two of 3 patients who died received no antifungal therapy before death. Thus, only 1 (2.94%) of 34 patients who received antifungal treatment (1 of 16 who received AmB) died.

In contrast, the previous review of C. lusitaniae fungemia listed death as the outcome for 7 (78%) of 9 patients [2]. In another review that was published in 1989 and that was limited to patients with C. lusitaniae fungemia, mortality was also quite high (7 [53.9%] of 13 patients) [3].

Previous work [2] suggests that the extremely high mortality rate associated with C. lusitaniae infection was in large part the result of AmB resistance that characterized the majority of infecting strains. The results of AmB susceptibility testing by a variety of methodologies have led to the unique characterization of C. lusitaniae isolates as resistant to AmB, unlike most other Candida species recovered from humans. In fact, it was stated previously [2, 1011] that AmB susceptibility may be “the exception rather than the rule.” In another report, the prevalence of AmB resistance was as high as 60% [31].

In our large review of isolate susceptibility, AmB resistance was much less common (21.7% of isolates). NCCLS-approved guidelines for performing antifungal susceptibility testing for Candida species were first available in 1997 [4]. These guidelines included recommendations for testing both azoles and 5-fluorocytosine. Although this document did not include recommendations for AmB testing, the methodologies have been used recently to examine AmB susceptibility. Regardless of the AmB susceptibility pattern seen in vitro, the pattern does not seem to correlate with the clinical responses to the drug in the present case series or that of a recent study of fungemia in cancer patients [29]. Additionally, the use of azoles, particularly fluconazole, for treating C. lusitaniae infection is increasing, and it was successful as monotherapy in 11 cases of deep-seated candidiasis described in the present series. Clearly, more study is needed to better define the most appropriate antifungal treatment of C. lusitaniae infections.

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C. lusitaniae and Fluconazole • CID 2003;36 (15 January) • e17

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