Candida sake candidaemia in non-neutropenic critically ill patients: a case series

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ABSTRACT

Candida sake infections are rare, but have been shown to cause severe infections including fungal endocarditis, peritonitis and bloodstream infection. As the reported incidence of *C. sake* candidaemia is very low, there is a dearth of data regarding the associated risk factors, antifungal agent-susceptibility patterns, optimal treatment policies, clinical course and outcomes of patients with such infections. We report a series of seven non-neutropenic intensive care unit patients with *C. sake* candidaemia. Most of the patients were men (6/7), were over 65 years of age (5/7) and had a history of recent hospitalisation (4/7) and comorbidities (4/7). However, all seven patients had a previous history of antibiotic uptake for more than 5 days and had a central venous catheter in situ at the time of taking specimens for culture. In four patients, infection was azole-resistant. Four patients required vasopressor support, three required mechanical ventilation and two required renal replacement therapy. Three of the seven patients died. This case series emphasises the importance of performing species identification and antifungal susceptibility testing in ICU patients with candidaemia, especially those with advanced age, underlying chronic diseases, indwelling vascular catheters, or a history of previous antibiotics or recent hospitalisations, as these patients may be at an increased risk of developing rare *Candida* infections like *C. sake*. Moreover, these rare *Candida* species may be more frequently resistant to azole antifungal agents, and may be associated with significant mortality.

Crit Care Resusc 2011; 13: 187–191

Candidaemia has been shown to be associated with high intensive care unit and hospital mortality rates, and has led to increased utilisation of limited resources.[1] Non-*albicans Candida* (NAC) species may be responsible for up to 65% of all candidaemia in the general patient population.[2] Moreover, the proportion of candidaemia caused by NAC species is increasing.[2-5] *Candida parapsilosis*, *Candida tropicalis*, *Candida krusei* and *Candida glabrata* are primarily responsible for a great proportion of the candidaemia caused by NAC species; other rare species like *Candida sake* contribute to less than 1% of such candidaemia.[2]

Certain risk factors have been identified with particular NAC species; for example, *C. parapsilosis* infection is more common among patients with hyperalimentation and foreign body insertion, and among neonates; *C. tropicalis* among patients with neutropenia or after bone marrow transplantation; *C. glabrata* among patients on azole prophylaxis, with urinary or vascular catheters or after surgery; *Candida lusitaniae* and *Candida guilliermondii* among patients with a history of previous polyene antifungal (amphotericin B or nystatin) use; and *Candida rugosa* among burns patients.[2] However, there is a dearth of data regarding risk factors associated with rare fungal infections like *C. sake*.

C. sake has rarely been shown to cause clinical infection; however, it has rarely been associated with severe infections, including endocarditis, peritonitis, and bloodstream infections.[4,6-9] The incidence of its isolation depends on which body part or fluid the specimens were collected from. A large study analysed data from 41 countries over 10.5 years and studied 256 882 isolates of *Candida* species collected from all body specimens. It found that the incidence of *C. sake* isolation ranged from zero to 0.08% over the different time periods.[3] Another large multicentre study, conducted over 10 years and spanning more than 32 countries, found only two cases of *C. sake* candidaemia among 6082 cases of candidaemia studied (an incidence of 0.0003%).[8] However, smaller studies involving 15–29 candidaemia patients have reported a much higher incidence of *C. sake* candidaemia, ranging from 3% to 7%.[4,9] Here, we report a series of seven non-neutropenic ICU patients with *C. sake* candidaemia and try to identify the risk factors associated with such infections.

Clinical records

Data were collected retrospectively from patients who were admitted to medical ICUs of a tertiary care centre over 4.5 years, from January 2007 to June 2011. The baseline clinical characteristics of the seven patients who developed *C. sake* candidaemia during this period are presented in Table 1. ICU course and antifungal susceptibility patterns are shown in Table 2 and Table 3, respectively. All seven patients had a previous history of antibiotic uptake for more than 5 days and had a central venous catheter (CVC) in situ at the time

Table 1. Baseline characteristics of patients with *Candida sake* candidaemia

Patient	Age in years; sex	Relevant comorbidities	Reason for ICU admission	Recent hospitalisation	Admission APACHE II score	PDR	SOFA score
1	74; male	Malignancy	Respiratory failure	Yes	15	21%	3
2	52; male	None	Hypotension	No	21	38.9%	10
3	66; male	Malignancy	Hypotension	Yes	13	16.5%	4
4	73; male	None	Altered sensorium	Yes	16	23.5%	6
5	31; male	Wegener granulomatosis	Respiratory failure	Yes	17	26.2%	9
6	78; female	None	Hypotension	No	27	60.5%	11
7	73; male	CKD	Hypotension	No	26	56.9%	7

APACHE = Acute Physiology and Chronic Health Evaluation. CKD = chronic kidney disease. PDR = predicted death rate. SOFA = Sequential Organ Failure Assessment.

of obtaining blood for culture, with a mean duration of 6.9 days (range, 2–11 days). The mean length of ICU stay was 21.3 days (range, 5–76 days) and mean length of hospital stay was 29.3 days (range, 5–76 days).

Patient 1

A 74-year-old man with a history of coronary artery disease and oesophageal cancer with liver metastases was admitted to ICU with progressive dyspnoea. He was found to have type 1 respiratory failure secondary to a respiratory infection and acute renal failure with metabolic acidosis. His condition was managed with non-invasive ventilation and intravenous cefoperazone–sulbactam and clindamycin. Urine output improved after fluid therapy.

On Day 6, a CVC was inserted in the patient's right internal jugular vein as he had difficult peripheral venous access. On Day 8, he developed a spiking fever with transient hypotension. Blood culture grew *C. sake*. Treatment with intravenous fluconazole was instituted, then changed to caspofungin on receipt of sensitivity report. The CVC was not removed as it had been inserted only 2 days previously. The patient's condition responded to the caspofungin, and he was discharged from the ICU to a general ward on Day 12.

Patient 2

A 52-year-old man with no comorbidities was admitted to ICU with fever, respiratory distress and hypotension. He was also found to have severe metabolic acidosis secondary to acute kidney injury. He was started on teicoplanin and imipenem, along with noradrenalin infusion through a CVC. Urine output improved after aggressive fluid therapy and the vasopressor was ceased on Day 2. On Day 3, he again became hypotensive and febrile.

Blood culture grew *C. sake*. Intravenous fluconazole was started, then changed to caspofungin according to the

Table 2. ICU course of seven patients with *Candida sake* candidaemia

Patient	Vasopressors	RRT	MV	ICU stay, days	Hospital stay, days	Outcome
1	No	No	No	12	21	Survived
2	Yes	No	No	9	12	Survived
3	No	No	No	18	27	Survived
4	No	No	No	14	24	Survived
5	Yes	Yes	Yes	76	76	Died
6	Yes	Yes	Yes	5	5	Died
7	Yes	No	Yes	15	40	Died

ICU = intensive care unit. MV = mechanical ventilation. RRT = renal replacement therapy.

Table 3. Patient factors and antifungal susceptibility patterns for patients with *Candida sake* candidaemia

Patient	Hospital stay before positive culture, days	Other positive sites	Previous antifungals	Resistant to
1	8	None	None	Azoles
2	3	None	None	Azoles
3	9	None	None	Azoles
4	19	Urine	None	None
5	53	Urine	Azoles	None
6	2	None	Azoles	None
7	25	Urine	Azoles	Azoles

sensitivity report. The CVC was not removed as it had been inserted only 3 days previously. The patient's condition responded to therapy, and he was discharged from the ICU to a general ward on Day 9.

Patient 3

A 66-year-old man with a history of squamous cell carcinoma of skin, interstitial lung disease, hypertension, and cerebrovascular accident was admitted to ICU with chest pain, progressive breathlessness and fever. He was found to have hypotension and type 2 respiratory failure. His condition was managed with non-invasive ventilation, intravenous fluids and broad-spectrum antibiotics (linezolid and cefoperazone–sulbactam). He had recurrent respiratory infections and intravenous catheter-associated sepsis, so cefoperazone–sulbactam was substituted with meropenem. Total parenteral nutrition (TPN) was also started through a CVC. Blood culture collected on Day 9 grew *C. sake*; the infection was initially managed with fluconazole, but later required treatment with amphotericin B. The patient's condition responded to therapy, and he was discharged from the ICU to a general ward on Day 18.

Patient 4

A 73-year-old man with a history of hypertension was admitted to ICU with acute stroke. On Day 9, he developed new-onset fever and his urine culture grew *Klebsiella pneumoniae*, which was treated with amikacin and cefoperazone–sulbactam. TPN was started as the patient was at high risk of aspiration. His condition improved gradually, but he developed another febrile episode on Day 19; blood and urine cultures taken at this time grew *C. sake*. The CVC was removed and intravenous fluconazole was started. The patient's condition responded to therapy, and he was discharged from the ICU to a general ward on Day 14.

Patient 5

A 31-year-old man with a history of Wegener granulomatosis, for which he was taking high doses of steroids and methotrexate, was admitted to ICU with complaints of fever and respiratory distress. He was empirically started on clarithromycin and cefoperazone–sulbactam. Polymerase chain reaction (PCR) of a throat swab sample was positive for H1N1 influenza (2009 pandemic strain). His condition was initially managed with non-invasive ventilation, but he subsequently required invasive mechanical ventilation. His clinical course was complicated by the development of a right pneumothorax. He also developed critical illness neuropathy, necessitating tracheostomy for anticipated prolonged mechanical ventilation.

He developed recurrent respiratory infections, and cultures of endotracheal secretions grew *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, for which multiple courses of antibiotics were given, including imipenem, amikacin, and polymyxin B. During his ICU stay, he also developed multiple episodes of hypotension, which required vasopressor support. The patient was started on fluconazole prophylaxis, as he was immunocompromised, had multiple indwelling catheters and was on multiple antibiotics for a prolonged period during his ICU stay.

Blood and urine cultures sent on Day 53 grew *C. sake*, for which intravenous fluconazole was started, and the urinary catheter and CVC were changed. The patient ultimately died from severe sepsis with multiorgan failure after a prolonged ICU stay.

Patient 6

A 78-year-old woman with no comorbidities was admitted to the ICU with dyspnoea, chest pain, fever and oliguria. She had to be immediately intubated and started on mechanical ventilation to treat type 1 respiratory failure and severe septic shock. Respiratory bacterial infection was treated with cefepime and clindamycin.

As the patient's condition continued to deteriorate rapidly, on Day 4, cefepime was replaced with imipenem, amphotericin B was added empirically and repeat blood cultures were sent, which grew *C. sake*. However, by the time the culture report became available, the patient had already died from severe sepsis and multiorgan failure.

Patient 7

A 73-year-old man with a history of non-insulin dependent diabetes mellitus type 2, diabetic nephropathy and coronary artery disease with severe left ventricular dysfunction was admitted with vomiting and abdominal pain and distension to a general ward, where his condition was managed conservatively with metronidazole and ofloxacin. On Day 7, a CVC was inserted for TPN after repeated attempts at starting enteral feeds failed. The CVC was changed on Day 18 as the patient developed new-onset fever, but blood cultures were sterile and fever subsided after catheter removal.

His hospitalisation was complicated by development of hospital-acquired pneumonia, so he was moved to the ICU on Day 25. On presentation to the ICU, he was found to be hypotensive and had severe metabolic acidosis. He was immediately intubated and started on mechanical ventilation in view of severe respiratory distress and septic shock. Blood and urine cultures grew *C. sake* that was resistant to azoles, so intravenous amphotericin B was started. However, the patient died from severe sepsis and multiorgan failure.

Discussion

In our case series of seven non-neutropenic ICU patients with *C. sake* candidaemia, most patients were men (6/7), most were more than 65 years of age (5/7) and most had a history of recent hospitalisation (4/7) and comorbidities (4/7). Moreover, all seven patients had a previous history of antibiotic therapy for more than 5 days and had a CVC in situ at the time of taking specimens for culture. Most patients (4/7) had azole-resistant infection, and three of the seven patients died.

Intensivists and other physicians may not be familiar with uncommon *Candida* species like *C. sake*. Moreover, there is a dearth of data regarding these species' antifungal susceptibility patterns, optimal treatment strategies, or prognosis. However, they may cause clinically significant infections, especially among critically ill ICU patients who are on multiple antibiotics and may have multiple indwelling catheters.

Patients on prior antimicrobial therapy, steroids or cytotoxic drugs, who had a CVC in situ, or with neutropenia or hyperalimentation, have been shown to be at higher risk for developing candidaemia.[9] Moreover, neutropenia, presence of CVC, mean number of antibiotics per day, recent prior gastrointestinal surgery, head trauma, bacterial sepsis and recent prior systemic antifungal exposure have been identified as risk factors for NAC.[10-13] All patients in our case series were on multiple antibiotics and had CVCs in place. In addition, some had recent exposure to antifungal agents. However, none of them were neutropenic at the time of developing *C. sake* candidaemia.

Azoles, such as fluconazole, remain the most commonly used antifungal agents for primary therapy of *Candida* bloodstream infections, even in ICU settings.[1] *C. sake* and other rare *Candida* species may be less susceptible to these systemic antifungal agents.[14] Moreover, an increase in fluconazole resistance has been shown over the years, specifically in *C. sake* isolates.[3] Most of our patients had azole-resistant *C. sake* infection. Owing to this high incidence of azole resistance among NAC species, it has been recommended to use a non-azole class antifungal agent like echinocandins or amphotericin B for patients at high risk of developing NAC bloodstream infection, especially until the pathogen causing candidaemia is determined.[5] Hence, isolation and early recognition of rare NAC species, which may have a higher incidence of azole resistance, may improve clinical management and patient outcome.

In our case series, however, the mortality in this subgroup of patients with azole-resistant candidaemia was lower than those patients with azole-sensitive *C. sake* candidaemia (1/4 v 2/3). This could be partially explained by the fact that appropriate therapy was instituted immediately, which could have prevented further complications and thereby improved outcome. This discrepancy could also be attributed to the small sample size of our cohort. Nonetheless, another study found that azole-resistant candidaemia among critically ill patients was not associated with higher mortality.[10]

Organ failures, including renal or cardiovascular failure and need for mechanical ventilation, have been shown to be independent risk factors for fatal candidaemia.[5,11] All of our patients who died required organ support, especially vasopressor or mechanical ventilatory support.

Certain NAC species may appear to be of lower virulence in animal models, but may have equal or greater virulence than *C. albicans* in humans.[2] The reported mortality due to infection with NAC species ranges from 15% to 35%, which is similar to that due to *C. albicans* infection. However, there may be differences in both overall and attributable mortality according to the particular species involved, with lowest mortality reported for *C. parapsilosis* and the highest for *C. tropicalis* and *C. glabrata* (up to 70%). Mortality associated with other NAC species is intermediate between these two extremes, and is comparable to that of *C. albicans*, in the range of 20%–40%.[2] The observed mortality of 43% in our patient series also corresponds to this range. Unsurprisingly, the mortality associated with NAC species has been shown to be highest among ICU and postsurgical patients.[2]

Conclusions

Bloodstream infections with rare *Candida* species may occur in ICU patients. Species identification and antifungal susceptibility testing is vital in patients with candidaemia as a significant proportion of these organisms may be resistant to the commonly used antifungals, the azoles, and hence these organisms may pose a threat to instituting optimal antifungal therapy and ensuring better patient outcome.

Competing interests

None declared.

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