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Candida tropicalis fungaemia: incidence, risk factors and mortality in a general hospital

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Abstract

The risk factors and clinical features of patients with *Candida tropicalis* fungaemia have not been fully defined. We performed a case–control study comparing 59 cases of *C. tropicalis* fungaemia with 177 episodes of fungaemia caused by other species of *Candida* in our hospital over a 24-year period (January 1985 to December 2008). Patients with *C. tropicalis* fungaemia were more likely to be older (median age, 67 vs. 56 years; p 0.01), to have cancer (45.5% vs. 31.6%, p 0.04), and to have the abdomen as the portal of entry (32.2% vs. 11.9%, p 0.001), and had a higher in-hospital mortality rate (61% vs. 44%, p 0.03). Multivariate analysis showed that the independent risk factors for *C. tropicalis* fungaemia were cancer (OR 4.5; 95% CI 1.05–3.83; p 0.03) and the abdomen as the portal of entry (OR 13.6; 95% CI 1.9–8.2; p <0.001). When survivors were compared with non-survivors, the risk factors associated with a poor outcome were neutropenia (19.4% vs. 0; p 0.03), corticosteroid treatment (36% vs. 13%; p 0.07), and septic shock (50% vs. 17.4%; p 0.01). The independent risk factors for mortality in the multivariate analysis were corticosteroid treatment (OR 8.2; 95% CI 0.9–27.7; p 0.04) and septic shock (OR 14.6; 95% CI 2.4–90.2; p 0.004), whereas urinary tract infection (OR 0.07; 95% CI 0.01–0.8; p 0.03) and catheter removal (OR 0.06; 95% CI 0.01–0.4; p 0.002) were protective factors. *C. tropicalis* is the fourth most common cause of fungaemia in our hospital. It is associated with underlying malignancy, the abdomen as the portal of entry, and poor outcome.

Keywords: *Candida tropicalis*, candidaemia, fungaemia, invasive candidiasis, non-*albicans Candida* species
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Introduction

Candidaemia is a major cause of morbidity and mortality in the healthcare setting. *Candida* species now rank fourth in the USA and sixth in Europe among causes of nosocomial bloodstream infection (BSI) [1–3]. In addition, the crude mortality rate of candidaemia is approximately 40–50%, depending on the population and the species studied [4–6].

In recent years, there has been an increase in the incidence of candidaemia and a shift towards *Candida* species other than *Candida albicans*, with *Candida parapsilosis*, *Candida glabrata*, *Candida krusei* and *Candida tropicalis* causing almost half of all episodes [5–12]. *C. parapsilosis* has been related to overuse of venous catheters, especially in neonates, transplant recipients, and patients receiving parenteral nutrition [13]. The emergence of *C. glabrata* and *C. krusei* has been related to antifungal exposure in specific populations, such as elderly patients, solid organ recipients, patients with neutropenia, patients receiving corticosteroids, and neonates [5]. In contrast, the clinical features of patients with candidaemia caused by *C. tropicalis* are poorly defined and usually biased by the selection of specific groups, such as patients with haematological malignancies or solid tumours [14–16]. In addition, data on incidence and mortality vary with the country and the population studied.

We performed the largest single-centre case–control study to date of patients with *C. tropicalis* fungaemia, in order to define the risk factors and outcome of this condition in an unselected population.

Materials and Methods

Study design and setting

We performed a case–control study comparing each patient who had had an episode of *C. tropicalis* fungaemia with three

cases of fungaemia caused by other species in our institution from January 1985 to December 2008. The controls were matched only by the year of isolation of non-*tropicalis Candida* species from blood, and were selected from the database by means of a random number table.

Ours is a large, general tertiary teaching hospital currently serving a population of approximately 750 000 inhabitants in Madrid, Spain. The hospital has approximately 1600 beds and all medical and surgical specialties, including solid organ (heart, liver, and kidney) and bone marrow transplant programmes.

Clinical data and definitions

The medical charts of the patients were retrospectively reviewed according to a pre-established protocol including the following variables: age, sex, underlying diseases, risk factors, clinical presentation, source of fungaemia, antifungal therapy, mortality during admission, and mortality attributable to candidaemia.

An episode of candidaemia was defined as at least one blood culture that was positive for *Candida*. Among underlying diseases, cancer refers to patients with an active tumour at the onset of candidaemia, haematological disease refers to patients with a haematological malignancy at the onset of candidaemia, human immunodeficiency virus (HIV) refers to patients with HIV infection, with or without AIDS, intravenous drug abuse (IVDA) refers to patients who were actively using illicit intravenous drugs at the onset of candidaemia, and transplantation refers to patients who were recipients of haematological or solid organ transplants.

Regarding risk factors, neutropenia refers to patients who presented an absolute neutrophil count <500 cells/mm^3 at the onset of candidaemia. Intensive-care unit stay, parenteral nutrition, intravenous lines and bladder catheters were considered to be risk factors if they were present at the onset of candidaemia. Corticosteroid use was assumed to be a risk factor if the patient had received ≥20 mg/day of prednisone for ≥15 days before the onset of fungaemia. Previous therapy with antimicrobials, antifungals and azoles was defined as the administration of one or more doses of each agent during the 30 days before the onset of candidaemia. Surgery refers to any type of major surgical procedure in the past 3 months.

With regard to clinical manifestations, fever was defined as an axillary temperature ≥38.3°C. Septic shock was defined as refractory hypotension despite adequate fluid resuscitation and cardiac output [17]. Renal failure was defined as a creatinine level ≥1.5 mg/dL.

The abdomen was considered to be the portal of entry in patients undergoing gastrointestinal surgery, patients undergoing peritoneal dialysis, and patients with an abdominal perforation and no other apparent source of BSI. For an episode to be included as catheter-related candidaemia, we followed the guidelines of the Infectious Diseases Society of America [18]. The urinary tract was considered to be the portal of entry in patients with obstructive uropathy and evidence of urinary tract infection caused by the same species of *Candida*.

We defined related mortality as death occurring within 5 days after diagnosis, with concurrent signs of active infection. Crude mortality was defined as mortality during admission.

Microbiological identification and antifungal susceptibility testing

From 1985 to October 1995, blood samples were processed with the automated BACTEC-NR system (Becton Dickinson, Cockeysville, MD, USA), and thereafter they were processed with the BACTEC-9240 system (Becton Dickinson). During the first period, all vials were incubated at 35°C for 7 days, and in the second period, vials were shaken continuously for 5 days. CHROMagar Candida (CHROMagar, Paris, France), a differential and selective chromogenic agar medium for yeasts, was introduced in our institution in 1995. Since then, the yeast isolates have been systematically subcultured onto CHROMagar Candida plates and incubated for 5 days at 35°C to identify possible mixed infections. Identification of the isolates was confirmed with the ID 32C system (bioMérieux, St Louis, MO, USA), according to the manufacturer's recommendations. Isolates recovered from blood cultures were stored at −70°C.

We studied the antifungal activity of amphotericin B, 5-fluorocytosine, ketoconazole, fluconazole, itraconazole, and voriconazole against the clinical isolates. The susceptibility study was performed with Sensititre YeastOne (Trek Diagnostic Systems, Cleveland, OH, USA), a modified microdilution method, according to the recommendations of the CLSI (M27-A2) [19,20]. The trays were incubated for 24–48 h at 35°C. Endpoint readings were defined visually as full inhibition of growth (amphotericin B) or prominent inhibition of growth (all other antifungals). We used the breakpoints proposed by CLSI M27-S3, as follows: fluconazole, susceptible ≤8 mg/L, susceptible–dose-dependent 16–32 mg/L,, and resistant ≥64 mg/L; voriconazole, susceptible ≤1 mg/L,, susceptible–dose-dependent 2 mg/L, and resistant ≥4 mg/L; caspofungin, susceptible ≤2 mg/L, and non-susceptible ≥4 mg/L; flucytosine, susceptible ≤4 mg/L, intermediate 8–16 mg/L, and resistant ≥32 mg/L; and itraconazole, susceptible ≤0.125 mg/L, susceptible–dose-dependent 0.25–0.5 mg/L, and resistant ≥1 mg/L.

Data analysis

We calculated the incidence of *C. tropicalis* fungaemia as the number of episodes detected each year divided by the number of inhabitants (in hundreds of thousands) in our reference area, and by the number of hospital admissions (in thousands). The incidence of *C. tropicalis* BSI during the study period was measured by use of the autoregressive integrated moving average test, with data in monthly intervals. This model was adjusted for the blood culture system used in each period and the percentage of blood cultures with growth of significant microorganisms (as a measurement of index of suspicion). A p-value <0.05 was considered to indicate significance. The analysis was carried out with SPSS 15.0 (SPSS, Chicago, IL, USA).

In the univariate analysis of cases and controls, categorical variables were compared by use of the chi-square test. Non-normally distributed continuous variables were compared by use of Student's *t*-test, and approximately normally distributed variables were compared by use of Student's *t*-test or analysis of variance. Stepwise logistic regression models were applied in the multivariate analysis to control for potential confounders and for risk factors of mortality. Variables with a p-value <0.1 in the univariate analysis were included in the multivariate models. Differences were considered to be significant for p-values <0.05. The analysis was carried out with SPSS 15.0 (SPSS).

Results

Between January 1985 and December 2008, we detected 970 episodes of fungaemia (3% of all episodes of significant BSI in our hospital): 448 were caused by *C. albicans*, 324 by *C. parapsilosis*, 78 by *C. glabrata*, 68 by *C. tropicalis*, 15 by *C. krusei*, and 37 by other species. The incidence of *C. tropicalis* BSI in our institution increased at an annual rate of 0.003 episodes/1000 admissions and 0.029 episodes/100 000 inhabitants, although the trend was not statistically significant (p 0.211 and p 0.116, respectively) (Table 1).

Of the 68 patients with *C. tropicalis* fungaemia, clinical data were fully available only for 59. These 59 patients (cases) were compared with 177 patients with fungaemia caused by other species (controls). In controls, the distribution of species was as follows: *C. albicans* in 67 patients (37.8%), *C. parapsilosis* in 40 (22.5%), *C. glabrata* in 37 (20.9%), mixed fungaemia in 14 (7.9%), *C. krusei* in 12 (6.7%), *Candida dubliniensis* in three (1.7%), *Candida guilliermondii* in two (1.1%), and *Saccharomyces cerevisiae* in two (1.1%).

Patients with *C. tropicalis* fungaemia were older (median, 67 vs. 56 years; p 0.01), had a higher incidence of cancer (49.2% vs. 32.8%; p 0.03) and had a lower incidence of HIV infection (5% vs. 17%; p 0.03) than controls (Table 2). No

TABLE 1. Episodes of fungaemia caused by *Candida tropicalis* during the study period expressed per population and per number of admissions

Year	Episodes of *C. tropicalis*	Inhabitants	*C. tropicalis* BSI per 100 000 inhabitants	Admissions	*C. tropicalis* BSI per 1000 admissions
1985	0	605 000	0	49 330	0
1986	0	608 594	0	50 365	0
1987	2	612 284	0.32	49 367	0.04
1988	1	615 974	0.16	48 558	0.02
1989	0	619 664	0	47 789	0
1990	6	623 354	0.96	46 443	0.13
1991	0	627 043	0	45 792	0
1992	2	629 040	0.31	45 565	0.04
1993	1	631 037	0.15	48 582	0.02
1994	3	633 034	0.47	48 275	0.06
1995	0	635 031	0	47 972	0
1996	4	637 028	0.62	49 687	0.08
1997	2	642 091	0.31	51 604	0.03
1998	3	647 154	0.46	50 371	0.06
1999	5	650 597	0.76	49 097	0.1
2000	5	653 849	0.76	50 873	0.09
2001	2	668 942	0.29	52 249	0.04
2002	3	684 754	0.43	52 889	0.05
2003	4	704 030	0.56	54 781	0.07
2004	3	717 326	0.41	61 299	0.05
2005	1	738 481	0.13	62 773	0.01
2006	9	743 387	1.21	65 681	0.13
2007	6	752 687	0.79	67 882	0.08
2008	6	777 784	0.77	58 724	0.1
Annual average	2.83	610 767	0.46	50 481	0.056
Annual increase	–	–	0.029	–	0.003
p	–	–	0.116	–	0.211

BSI, bloodstream infection.

TABLE 2. Comparison between the patients with *Candida tropicalis* fungaemia and the patients with fungaemia caused by other species

Factor	*C. tropicalis* fungaemia (*n* = 59)	Fungaemia caused by other species (*n* = 177)	p	Multivariate analysis, OR (95% CI), p
Age (years), mean ± SD (median, range)	59 ± 23 (67, 0–90)	49 ± 25 (56, 0–90)	0.01	
Gender, no. (%)				
Male	40 (67.8)	119 (67.2)	1	
Female	19 (32.2)	58 (32.8)		
Underlying disease, no. (%)				
Cancer	29 (49.2)	58 (32.8)	0.03	4.5 (1.05–3.83), 0.03
Haematological disease	6 (10.2)	16 (9)	0.76	
HIV	3 (5.1)	30 (17)	0.03	
Injection drug use	4 (6.8)	21 (12)	0.33	
Transplantation	3 (5.1)	12 (7.1)	0.76	
Risk factor, no. (%)				
Intensive-care unit	15 (25.4)	55 (31.1)	0.45	
Neutropenia	7 (11.9)	13 (7.3)	0.27	
Surgery	28 (47.5)	85 (48)	1	
Parenteral nutrition	29 (49.2)	87 (49.2)	1	
Intravenous lines	49 (83.1)	154 (87)	0.51	
Bladder catheter	39 (66.1)	117 (66.1)	1	
Previous antimicrobials	48 (81.4)	143 (80.8)	1	
Previous antifungals	11 (18.6)	55 (31.1)	0.07	
Previous azole agents	10 (16.9)	42 (23.7)	0.36	
Corticosteroids	16 (27.1)	44 (24.9)	0.76	
Clinical manifestations, no. (%)				
Fever	46 (78)	146 (82.5)	0.44	
Shock	22 (37.5)	53 (29.9)	0.33	
Renal insufficiency	13 (22)	23 (13)	0.09	
Source, no. (%)				
Abdomen	19 (32.2)	21 (11.9)	0.001	13.6 (1.9–8.2), <0.001
Venous catheter	14 (23.7)	78 (44)	0.006	
Unknown	18 (30.5)	54 (30.5)	1	
Urine	7 (12)	11 (6.2)	0.16	
Positive culture from sites other than blood, no. (%)				
Urine	15 (25.4)	31 (17.5)	0.19	
Venous catheter	11 (18.6)	49 (27.7)	0.23	
Respiratory sample[a]	4 (6.8)	21 (11.9)	0.34	
Abdominal sample[b]	3 (5.1)	13 (7.3)	0.76	
Wound	2 (3.4)	19 (10.7)	0.11	
Cardiac valve	1 (1.7)	1 (0.6)	0.44	
Metastatic complications, no. (%)				
Skin and soft tissue	2 (3.4)	11 (6.2)	0.53	
Ocular	1 (1.7)	11 (6.2)	0.30	
Lung	2 (3.4)	6 (3.4)	1	
Endocarditis	1 (1.7)	3 (1.7)	1	
Liver	0	2 (1.1)	1	
CNS	0	2 (1.1)	1	
Received antifungal therapy, no. (%)	38 (64.4)	140 (79.1)	0.03	
Time to treatment (days), mean ± SD (median, range)	0.95 ± 3.7 (1, −12 to 8)	1.02 ± 6.4 (2, −35 to 19)	0.9	
Catheter withdrawal, no. (%)	25 (42.4)	93 (52.5)	0.2	
Mortality, no. (%)	36 (61)	78 (44)	0.03	
Related mortality, no. (%)	18 (30.5)	52 (29.4)	0.87	

CNS, central nervous system; HIV, human immunodeficiency virus; SD, standard deviation.
[a]Respiratory samples include sputum (12), tracheobronchial aspirate (11), and pleural fluid (two).
[b]Abdominal samples include peritoneal fluid (nine), intra-abdominal abscess drainage (five), and biliary fluid (two).

significant differences were found between the groups for other risk factors and clinical manifestations. The most common portals of entry were the abdomen among the cases (32.2% vs. 11.9%; p 0.001) and a venous catheter among the controls (23.7% vs. 44%; p 0.006). In 125 patients, the same *Candida* species was isolated from sites other than blood, with the same frequencies in cases and controls (49.2% vs. 54.2%; p 0.55). No significant differences were found between the groups for metastatic complications. With regard to antifungal treatment, we found that the cases were less likely to have received treatment (64.4% vs. 79%; p 0.03). In 14 of the 21 untreated cases, antifungal therapy was not started because the patient died before or on the day when blood cultures became positive, or because the prognosis was extremely poor. In-hospital mortality was higher among patients with *C. tropicalis* fungaemia than among controls (61% vs. 44%; p 0.03), and related mortality rates were similar between the groups (30.5% vs. 29.4%; p 0.87). The median time to death was 9 days (range, 0–74 days) among patients with *C. tropicalis* fungaemia vs. 10 days (range, 0–140 days) among those with fungaemia caused by other species (p 0.56). The overall mortality rates at 15 and 30 days after the diagnosis of candidaemia were 64% and 80.6% among patients with *C. tropicalis* fungaemia vs. 68% and

84.6% among those with fungaemia caused by other species (p 0.6).

The multivariate analysis revealed that the factors independently associated with *C. tropicalis* fungaemia were cancer (OR 4.5; 95% CI, 1.05–3.83; p 0.03) and the abdomen as the portal of entry (OR 13.6; 95% CI 1.9–8.2; p <0.001). Of the 28 patients with cancer, 16 (57.1%) had gastrointestinal involvement. Among the 19 patients in whom the abdomen was the portal of entry, surgery (73.7%) and solid tumour (57.1%) were the most common underlying conditions. Nine patients underwent surgery for gastrointestinal cancer.

We also compared episodes of fungaemia caused by *C. tropicalis* and *C. albicans* (Table 3). Patients with *C. tropicalis* fungaemia were less frequently infected with HIV, and the source was less commonly an intravenous catheter.

Susceptibility testing was performed on the 68 available *C. tropicalis* strains (Table 4). With the exception of one isolate that was resistant to flucytosine, all isolates were susceptible to the antifungal agents studied.

In order to analyse the factors associated with mortality among patients with *C. tropicalis* fungaemia, we compared survivors with non-survivors. The univariate analysis showed that neutropenia (19% vs. 0%; p 0.03), corticosteroid treatment (36% vs. 13%; p 0.07) and septic shock (50% vs. 17.4%; p 0.01) were more common among non-survivors (Table 5), whereas HIV infection (0% vs. 13%; p 0.05), IVDA (0% vs. 17.4%;

TABLE 3. Comparison between the patients with *Candida tropicalis* fungaemia and the patients with *Candida albicans* fungaemia

Factor	*C. tropicalis* fungaemia (*n* = 59)	*C. albicans* fungaemia (*n* = 67)	p	Multivariate analysis, OR (95% CI), p
Age (years), mean ± SD (median, range)	59 ± 23 (67, 0–90)	50 ± 24 (55, 0–90)	0.04	
Gender, no. (%)				
Male	40 (67.8)	48 (71.6)	0.69	
Female	19 (32.2)	19 (28.4)		
Underlying disease, no. (%)				
Cancer	29 (49.2)	21 (31.3)	0.05	
Haematological disease	6 (10.2)	4 (6)	0.5	
HIV	3 (5.1)	17 (25.4)	0.003	0.17 (0.04–0.62), 0.008
Injection drug use	4 (6.8)	11 (16.4)	0.108	
Transplantation	3 (5.1)	2 (3)	0.66	
Risk factor, no. (%)				
Intensive-care unit	15 (25.4)	24 (35.8)	0.25	
Neutropenia	7 (11.9)	1 (1.5)	0.02	
Surgery	28 (47.5)	29 (43.3)	0.72	
Parenteral nutrition	29 (49.2)	34 (50.7)	1	
Intravenous lines	49 (83.1)	60 (89.2)	0.31	
Bladder catheter	39 (66.1)	43 (64.2)	0.85	
Previous antimicrobials	48 (81.4)	53 (79)	0.82	
Previous antifungals	11 (18.6)	17 (25.4)	0.39	
Previous azole agents	10 (16.9)	12 (17.9)	1	
Corticosteroids	16 (27.1)	10 (14.9)	0.12	
Clinical manifestations, no. (%)				
Fever	46 (78)	58 (86.6)	0.24	
Shock	22 (37.5)	17 (25.4)	0.18	
Renal insufficiency	13 (22)	6 (9)	0.05	
Source, no. (%)				
Abdomen	19 (32.2)	11 (16.9)	0.06	
Venous catheter	14 (23.7)	30 (44.8)	0.02	0.42 (0.18–0.94), 0.035
Unknown	18 (30.5)	16 (23.9)	0.42	
Urine	7 (12)	4 (6)	0.34	
Positive culture from sites other than blood, no. (%)				
Urine	15 (25.4)	12 (18)	0.38	
Venous catheter	11 (18.6)	18 (27)	0.29	
Respiratory sample[a]	4 (6.8)	10 (15)	0.16	
Abdominal sample[b]	3 (5.1)	4 (6)	1	
Wound	2 (3.4)	7 (10.4)	0.17	
Cardiac valve	1 (1.7)	0	0.47	
Metastatic complications, no. (%)				
Skin and soft tissue	2 (3.4)	4 (6)	0.68	
Ocular	1 (1.7)	5 (7.5)	0.21	
Lung	2 (3.4)	1 (1.5)	0.59	
Endocarditis	1 (1.7)	1 (1.5)	1	
Liver	0	1 (1.5)	1	
Received antifungal therapy, no. (%)	38 (64.4)	55 (82)	0.03	
Time to treatment (days), mean ± SD (median, range)	0.95 ± 3.7 (1, −12 to 8)	2.65 ± 5.1 (3,−1 to 19)	0.09	
Catheter withdrawal, no. (%)	25 (42.4)	30 (44.8)	0.85	
Mortality, no. (%)	36 (61)	30 (44.8)	0.07	
Related mortality, no. (%)	18 (30.5)	5 (7.5)	0.16	

HIV, human immunodeficiency virus; SD, standard deviation.
[a]Respiratory samples include sputum (six), tracheobronchial aspirate (six) and pleural fluid (two).
[b]Abdominal samples include peritoneal fluid (three) and intra-abdominal abscess drainage (four).

TABLE 4. Susceptibility of the 68 available *Candida tropicalis* strains

		MIC (mg/L)			
Antifungal drug	**No. of isolates**	**50%**	**90%**	**Geometric mean**	**Range of MICs**
Amphotericin B	68	1	1	0.798	0.016–4
Fluconazole	68	0.25	2	0.965	0.06–8
Itraconazole	68	0.125	0.25	0.160	0.004–2
Voriconazole	68	0.03	0.125	0.049	0.004–0.5
Posaconazole	17	0.061	0.25	0.082	0.016–0.25
Caspofungin	29	0.06	0.25	0.092	0.006–0.5
Flucytosine	68	0.125	0.25	0.529	0.016–32

TABLE 5. Comparison between survivors and non-survivors among patients with *Candida tropicalis* fungaemia

Factor	**Non-survivors (*n* = 36)**	**Survivors (*n* = 23)**	**p**	**Multivariate analysis, OR (95% CI), p**
Age (years), mean ± SD (median, range)	61 ± 21 (67, 0–90)	55 ± 27 (68, 1–89)	0.31	
Gender, no. (%)				
Male	25 (69.84)	15 (65.2)	0.7	
Female	11 (30.6)	8 (34.8)		
Underlying disease, no. (%)				
Cancer	19 (52.8)	9 (39.1)	0.42	
Haematological disease	6 (16.7)	0	0.07	
HIV	0	3 (13)	0.05	
Injection drug use	0	4 (17.4)	0.02	
Transplantation	3 (8.3)	0	0.27	
Risk factor, no. (%)				
Intensive-care unit	12 (33.3)	3 (13)	0.12	
Neutropenia	7 (19.4)	0	0.03	
Surgery	15 (41.7)	13 (56.5)	0.3	
Parenteral nutrition	17 (47.2)	12 (52.2)	0.8	
Intravenous lines	30 (83.3)	19 (82.6)	1	
Bladder catheter	24 (66.7)	15 (65.2)	1	
Previous antimicrobials	28 (77.8)	20 (87)	0.5	
Previous antifungals	7 (19.4)	4 (17.4)	1	
Previous azole agents	6 (16.7)	4 (17.4)	1	
Corticosteroids	13 (36.1)	3 (13)	0.07	8.2 (1.1–61.9), 0.04
Clinical manifestations, no. (%)				
Fever	27 (75)	19 (82.6)	0.54	
Shock	18 (50)	4 (17.4)	0.01	14.6 (2.4–90.2), 0.04
Renal insufficiency	8 (22.2)	5 (21.7)	1	
Source, no. (%)				
Abdomen	14 (38.9)	5 (21.7)	0.25	
Catheter	6 (16.7)	8 (34.8)	0.13	
Unknown	13 (36.1)	5 (21.7)	0.38	
Urine	2 (5.6)	5 (21.7)	0.09	0.07 (<0.01–0.8), 0.03
Received therapy, no. (%)	22 (61.1)	15 (65.2)	0.79	
Time to treatment (days), mean ± SD (median, range)	0.5 ± 4.4 (2, −12 to 6)	1.6 ± 2.3 (1, −2 to 8)	0.38	
Catheter withdrawal, no. (%)	10 (27.8)	15 (65.2)	0.007	0.06 (0.01–0.4), 0.002

HIV, human immunodeficiency virus; SD, standard deviation.

p 0.01), the urinary tract as the portal of entry (5.6% vs. 21.7%; p 0.09) and venous catheter removal (28% vs. 65%; p 0.007) were associated with a lower mortality rate. In the multivariate analysis, corticosteroid treatment (OR 8.2; 95% CI 1.1–61.9; p 0.04) and septic shock (OR 14.6; 95% CI 2.4–90.2; p 0.004) proved to be independent risk factors for death. The urinary tract as the portal of entry (OR 0.07, 95% CI <0.01–0.8; p 0.03) and venous catheter removal (OR 0.06, 95% CI 0.01–0.4; p 0.002) were protective factors.

Discussion

C. tropicalis caused 6% of all episodes of fungaemia in our institution during the study period. Patients with *C. tropicalis* fungaemia were older, suffered more frequently from cancer, and had a higher mortality rate than patients with fungaemia caused by other species.

The proportion of candidaemia episodes caused by *C. tropicalis* varies widely with geographical area, ranging from 4% to 24% of all episodes of candidaemia [5,6,8,21–23]. *C. tropicalis* accounts for up to 36% of episodes in South America, the Middle East, and Southeast Asia [21–25]. By contrast, in North America and Europe, *C. tropicalis* fungaemia usually accounts for 4–16% of all episodes of candidaemia [5,6,8,12]. The reasons for these differences are not clear, although they may be attributable to the greater use of fluconazole in hospitals in the USA and Europe [21,26], or to a widespread clone of this species in the other countries [27–29].

In our institution, previous azole use was similar between patients with *C. tropicalis* fungaemia and those with fungaemia caused by other species (27% vs. 25%; p 0.7), although we

were unable to demonstrate an accumulation of episodes during the study period.

An association between *C. tropicalis* fungaemia and cancer has been reported [12,21,25], although most studies included only patients with cancer as an underlying disease or only compared *C. tropicalis* fungaemia with *C. albicans* fungaemia [16,21]. Our study is a better reflection of clinical practice, as we compared an unselected population of patients with *C. tropicalis* fungaemia with patients who had fungaemia caused by other *Candida* species. *C. tropicalis* patients were more likely to be older, suffer from cancer, and have the abdomen as the portal of entry. Neutropenia was not associated with *C. tropicalis*, and a venous catheter was a less common source of this species. Our multivariate analysis showed cancer and the abdomen as the portal of entry to be independent risk factors for *C. tropicalis* fungaemia. Most of the episodes of *C. tropicalis* fungaemia that we detected were associated with gastrointestinal tumours and had an intra-abdominal origin.

We found that the mortality rate during admission of patients with *C. tropicalis* fungaemia was higher than that of controls (61% vs. 44%; p 0.03), and similar data have been reported by other authors [6,12]. In a population-based surveillance study of candidaemia performed in Barcelona from 2002 to 2003, Almirante *et al.* [12] found that patients who had *C. tropicalis* fungaemia were more likely to die within 30 days than those who did not (59% vs. 42%; p 0.06). On comparison of survivors with non-survivors in an intensive-care cohort, the isolation of *C. tropicalis* increased the risk of dying 2.6-fold, although the difference did not reach statistical significance (p 0.09) [6].

We found that corticosteroid therapy and septic shock were independent risk factors for mortality. The urinary tract as the portal of entry and removal of the venous catheter proved to be protective factors. These results agree with those of other studies that have analysed risk factors for in-hospital mortality among patients with candidaemia caused by all types of *Candida* species [6,30]. In a hospital cohort, the independent determinants of mortality were corticosteroid use, increasing APACHE II score, inadequate initial fluconazole dosing, and retention of a central venous catheter [30]. In an intensive-care cohort, the mortality rate was higher when the central venous catheter was removed ≥2 days after the diagnosis of candidaemia (60.9% vs. 39.4% with removal within 1 day; p 0.04) [6].

The limitations of our study include its retrospective design. However, cases and controls were representative of the general population of patients with fungaemia at our hospital during the study period. The small number of patients may limit the conclusions that can be drawn about the prognostic factors. However, as we mentioned above, fungaemia caused by *C. tropicalis* is not very prevalent in Europe. In a large population-based study, *C. tropicalis* caused only 10% of 345 episodes of candidaemia [12], and in the intensive-care cohort of Leroy *et al.* [6], only 15 (4.9%) of the 271 invasive candidiasis episodes were caused by *C. tropicalis*. So, to our knowledge, this is the largest series of *C. tropicalis* fungaemia from Europe. Another issue is that we did not perform superficial cultures to check for *Candida* colonization, so we could not determine whether prior superficial colonization was more common among patients who developed *C. tropicalis* fungaemia.

C. tropicalis is a relevant cause of fungaemia, and should alert physicians to the possibility of underlying malignancy, abdominal origin, and poor prognosis.

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Transparency Declaration

This study does not present any conflict of interest for the authors.

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