ORIGINAL ARTICLE

# Risk factors for late recurrent candidaemia. A retrospective matched case–control study

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## Abstract

Incidence, risk factors and clinical significance of late recurrent (LR) candidaemia (>1 month between episodes) remains unclear. The 1219 episodes of candidaemia detected from January 1985 to December 2014 were reviewed. We selected all cases with more than one episode separated by at least 30 days after clinical resolution in the interim (cases) and compared each of them with two controls (patients with single episodes of candidaemia). Clinical strains were genotyped to differentiate relapses from re-infection. Eighteen patients (1.48%) had 36 episodes of LR candidaemia (median 4 months). Independent risk factors for recurrence in the multivariate analysis were: underlying gastrointestinal disease (OR 67.16; 95% CI 5.23–861.71; p 0.001) and fungaemia due to *Candida parapsilosis* (OR 9.10; 95% 1.33–62.00; p 0.02). All episodes of LR candidaemia diagnosed during the first 3 months were due to an intravascular source of infection, whereas in those occurring after 3 months the main source of the disease was the abdomen, followed by endocarditis, and urinary tract. Molecular typing showed that 42.9% of LR candidaemias were relapses and 57.1% were re-infections. Neither time of recurrence nor clinical origin could predict type of recurrence. LR candidaemia is a relatively rare event that is more frequent in patients who have an initial episode of candidaemia due to *C. parapsilosis* or an underlying gastrointestinal disease. Episodes of LR candidaemia that occur within the first 3 months should prompt an attempt to exclude an intravascular source of infection, whereas those occurring later point to an intra-abdominal origin.



**Keywords:** *Candida* endocarditis, candidaemia, candidiasis, invasive disease, recurrent infection
**Original Submission:** 28 July 2015; **Revised Submission:** 8 October 2015; **Accepted:** 21 October 2015
Editor: E. Roilides
**Article published online:** 5 November 2015

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## Introduction

Recurrent bloodstream infections (BSIs) caused by the same microorganism are uncommon [1,2] and may occur early (<1 month between episodes) [3,4] or late (>1 month between episodes) [5–9]. Early recurrence is usually attributed to non-resolution of the underlying clinical condition or to inappropriate antimicrobial therapy [3,4], but the significance of late recurrence has received less attention and only episodes caused by a few specific bacteria have been studied. Late recurrence has been reported in 2.1%–9.4% of Gram-positive BSIs [5–8,10,11] and in 6%–13.3% of Gram-negative BSIs [2,9,12].

Information regarding late recurrence of candidaemia is even scarcer. To our knowledge, only one retrospective study [13] and a limited number of single cases [14–16] or very short case series [17,18] have specifically addressed this issue. However, data on the incidence [17,19], underlying conditions



http://dx.doi.org/10.1016/j.cmi.2015.10.023

[19], and risk factors for late recurrent (LR) candidaemia [14–16,19] were not included in all studies.

We performed a large, single-centre, case–control study of patients with LR candidaemia in order to define risk factors, clinical significance and outcome.

## Materials and Methods

### Study design and setting

We performed a retrospective case–control study (ratio 1 : 2) at a 1550-bed tertiary institution with a full range of clinical services attending a population of approximately 715 000 inhabitants. All patients with at least one episode of BSI due to *Candida* spp. diagnosed during the period January 1985 to December 2014 were potentially eligible for the study.

The cases comprised patients with LR candidaemia who had had at least two episodes of candidaemia ≥30 days apart with clinical and microbiological resolution in the interim. The control group comprised patients who were randomly chosen from among patients who had survived an episode of candidaemia within the same year as the cases and had no further blood cultures positive for *Candida* spp. The characteristics of the first episodes of candidaemia were compared. Patients with either prolonged episodes of candidaemia (successive blood cultures positive for *Candida* spp.) or early recurrence (recurrence <30 days after cure) were excluded.

The Ethics Committee of our centre (Comité ético de Investigación Clínica del Hospital General Universitario Gregorio Marañón) approved the study.

### Clinical data and definitions

The medical history was retrospectively reviewed according to a pre-established protocol including the following variables: age, sex, underlying diseases, risk factors for candidaemia, clinical presentation, source of fungaemia, *Candida* species, antifungal therapy and catheter withdrawal.

An episode of candidaemia was defined as at least one peripheral blood culture positive for *Candida* spp. All isolates from blood from the same patient within 1 week were considered a single episode.

Late recurrent candidaemia was further classified as relapse or re-infection. We considered re-infections all episodes caused by different *Candida* species or, if the episode was caused by the same species, then both isolates had to be genetically different. Relapses were episodes caused by the same genus and species. Genotyping results were only available for *Candida albicans* and *Candida parapsilosis*.

Gastrointestinal diseases included inflammatory bowel disease, intestinal obstruction, ischaemia and/or malignancy in the gastrointestinal tract. Immunosuppression included malignancy, haematological disease, human immunodeficiency virus infection, or transplantation (haematopoietic stem cells or solid organs). Malignancy was defined as a neoplasm that was active at the time of the episode of candidaemia.

We defined a series of risk factors: neutropenia was defined as an absolute neutrophil count <500 cells/mm$^3$ at the onset of candidaemia. 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 included any major surgical procedure in the previous 3 months.

As for clinical manifestations, fever was defined as an axillary temperature ≥38.3°C. Septic shock was defined as refractory hypotension despite adequate fluid resuscitation. 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 or peritoneal dialysis and in patients with an abdominal perforation and no other apparent source of BSI. As suggested by the guidelines of the Infectious Diseases Society of America, an episode of candidaemia could only be considered catheter-related if the catheter tip culture was positive with the same *Candida* species [20]. 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*. Endovascular prostheses were considered the portal of entry in patients who had no other apparent source of BSI. One-year mortality after the last index *Candida* spp. blood culture collection was recorded.

Source control of infection was considered adequate if, within 48 h from blood culture collection, any central venous catheters were removed or when a surgical or radiological procedure to drain fluid collection or abscess was performed.

### Microbiological identification

Blood samples were obtained for culture using standard procedures. From 1985 to 1995, samples were processed with the automated BACTEC-NR system (Becton Dickinson, Cockeysville, MD, USA) and thereafter using the BACTEC-9240 system (Becton Dickinson). During the first period, all vials were incubated at 35°C for 7 days; during the second period, vials were shaken continuously for 5 days. CHROMagar *Candida* (CHROMagar, Paris, France), a differential and selective chromogenic agar medium for yeast isolates, was introduced in our institution in 1995. Since then, yeast isolates have been

systematically subcultured on to CHROMagar *Candida* plates and incubated for 5 days at 35°C to identify possible mixed infections. Identification of the isolates was confirmed using the ID 32C system (bioMerieux, St Louis, MO, USA). Isolates recovered from blood were stored at −70°C.

### Molecular typing

Isolates were cultured on CHROMagar *Candida* agar plates for presumptive identification at species level. Further molecular identification of the isolates was performed after amplification and sequencing of the ITS1-5.8S-ITS2 region. Before genotyping, isolates were subcultured on Sabouraud agar. The *C. albicans* strains were genotyped using a panel of six previously described microsatellite markers [21,22]. *Candida parapsilosis* isolates were genotyped using four microsatellite markers described by Sabino *et al.* and Vaz *et al.* [23,24]. Capillary electrophoresis was carried out in a 3130xl analyser (Applied Biosystems, Inc., Foster City, CA, USA). Allele sizes were automatically determined using GeneMapper 4.0. Typing data were entered into BioNumerics 6.0.1. Isolates from a single patient matched when they showed exactly the same alleles for all loci analysed.

### Data analysis

We calculated the incidence of LR candidaemia as the number of episodes detected per 100 000 hospital admissions. In the univariate analysis of cases and controls, categorical variables were compared using the chi-square test. Non-normally distributed continuous variables were compared using the *t*-test, and normally distributed variables were compared using the *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 LR candidaemia. Variables with a p-value <0.1 in the univariate analysis were included in the multivariate models. Differences were considered to be significant for $p < 0.05$. The analysis was carried out with SPSS 18.

## Results

Between January 1985 and December 2014 (30 years), 1219 patients developed candidaemia at our institution (*C. albicans* 46.4%, *C. parapsilosis* 30.7%, *Candida glabrata* 9.2%, *Candida tropicalis* 7.7% and other species 6%), and 71 had more than one episode (positive BCs more than 1 week apart). Of those, 53 corresponded either to prolonged episodes of candidaemia or to early recurrences and were excluded. The remaining 18 patients fulfilled the criteria for LR candidaemia and are the object of the present study. Patients with LR candidaemia represented 1.48% of all patients with candidaemia (1.15 episodes per 100 000 admissions).

### Comparison of LR candidaemia with non-recurrent candidaemia

Complete clinical information was available for 16 of the 18 patients with LR candidaemia. Patients with LR candidaemia (cases) were compared with 32 randomly chosen patients with non-recurrent candidaemia (controls) (Table 1). At univariate analysis, characteristics significantly more common among patients with LR candidaemia were underlying gastrointestinal diseases (56.2% versus 3.1%, $p < 0.001$), septic shock (43.8% versus 12.5%, p 0.03) and fungaemia caused by *C. parapsilosis* (50% versus 18.8%, p 0.04). One-year mortality was 50% for patients with LR candidaemia compared with 25% for control patients (p 0.11). No further significant differences were found between groups regarding demographic characteristics, risk factors, source of the disease, or adequate management of candidaemia. Antifungal resistance was not an issue predisposing to second episodes, as all patients had susceptible strains and received adequate antifungal treatment.

A logistic regression model was constructed to evaluate independent predictors for LR candidaemia (Table 2). After adjusting for age and sex, two factors remained significantly and independently associated with the development of LR candidaemia: *C. parapsilosis* fungaemia (OR 9.10; 95% 1.33–62.00) and gastrointestinal disease as underlying condition (OR 67.16; 95% CI 5.23–861.71). The Hosmer–Lemeshow goodness of fit test results indicate that the LR candidaemia model reflected the data well (p 0.80).

### Characteristics of LR candidaemia according to time to recurrence and *Candida* species

Clinical characteristics of patients with LR candidaemia are presented in Table 3. Median time between the first episode and the late recurrence was 4 months (range, 1 month to 3 years). Interestingly, all episodes diagnosed during the first 3 months were due to an intravascular infection (thrombophlebitis, endocarditis, or catheter-related infection), whereas the main source of the recurrences that occurred after 3 months was the abdomen, followed by endocarditis and the urinary tract (see Fig. 1).

We were not able to find a relationship between species and time of recurrence or with the clinical manifestation of the disease (data not shown).

### Classification of LR candidaemias into relapses or re-infections

We analysed the genotype of the isolates from 14 patients with LR candidaemia caused by *C. albicans* or *C. parapsilosis*. Six cases corresponded to relapses (42.9%) and eight to re-infections (57.1%). Four re-infections were caused by different species

**TABLE 1. Comparison of patients with candidaemia who developed late recurrence (cases) or had single episode (controls)**

| Variables | Recurrent episodes[a] (*n* = 16) | Controls (*n* = 32) | p |
|---|---|---|---|
| Age (years), mean ± SD | 49 ± 29.1 | 63 ± 49 | 0.07 |
| Male, *n* (%) | 10 (62.5) | 21 (65.6) | 1 |
| Department, *n* (%) | | | |
| Adult intensive care unit | 6 (37.5) | 8 (25.0) | 0.50 |
| Paediatric intensive care unit | 4 (25.0) | 2 (6.2) | 0.09 |
| Medical | 1 (6.2) | 9 (28.1) | 0.13 |
| Oncology-haematology | 1 (6.2) | 4 (12.5) | 0.65 |
| Surgery | 4 (25.0) | 9 (28.1) | 1 |
| Underlying disease, *n* (%) | | | |
| Immunosuppression | 6 (37.5) | 17 (53.1) | 0.36 |
| Cardiovascular disease | 6 (37.5) | 15 (46.9) | 0.76 |
| Malignancy | 6 (37.5) | 14 (43.8) | 0.76 |
| Diabetes mellitus | 1 (6.2) | 8 (25.0) | 0.23 |
| Liver disease | 1 (6.2) | 3 (9.4) | 1 |
| Transplantation | 0 (0) | 2 (6.2) | 0.54 |
| Gastrointestinal disease | 9 (56.2) | 1 (3.1) | <0.001 |
| Risk factor, *n* (%) | | | |
| Neutropenia | 0 (0) | 1 (3.1) | 1 |
| Surgery | 13 (81.2) | 21 (65.6) | 0.32 |
| Total parenteral nutrition | 12 (75) | 14 (43.8) | 0.07 |
| Central venous catheter | 14 (87.5) | 28 (87.5) | 1 |
| Bladder catheter | 9 (56.2) | 14 (43.8) | 0.54 |
| Previous antimicrobials | 15 (93.8) | 32 (100) | 0.33 |
| Previous antifungals | 10 (62.5) | 10 (31.3) | 0.07 |
| Intensive care unit stay | 1 (6.2) | 6 (18.8) | 0.40 |
| Corticosteroids | 1 (6.2) | 6 (18.8) | 0.40 |
| Clinical manifestation, *n* (%) | | | |
| Fever | 16 (100) | 26 (81.3) | 0.16 |
| Presentation with septic shock | 7 (43.8) | 4 (12.5) | 0.03 |
| Renal insufficiency | 3 (18.8) | 10 (31.3) | 0.49 |
| Source, *n* (%) | | | |
| Abdomen | 3 (18.8) | 6 (18.8) | 1 |
| Central venous catheter | 10 (62.5) | 17 (53.0) | 0.75 |
| Primary | 2 (12.5) | 4 (12.5) | 1 |
| Urine | 1 (6.2) | 5 (15.6) | 0.64 |
| Time between hospitalization and onset of candidaemia (days), median (interquartile range) | 26.5 (9.2–34.5) | 20 (8.5–31.2) | 0.47 |
| Metastatic complication, *n* (%) | | | |
| Skin and soft tissue | 1 (6.2) | 0 | 0.33 |
| Eye | 3 (18.8) | 1 (3.1) | 0.1 |
| Other | 2 (12.5) | 5 (15.6) | 1 |
| *Candida* species, *n* (%) | | | |
| *C. albicans* | 5 (31.2) | 16 (50) | 0.35 |
| *C. parapsilosis* | 8 (50.0) | 6 (18.8) | 0.04 |
| *C. tropicalis* | 2 (12.5) | 6 (18.8) | 0.71 |
| *C. orthoparapsilosis* | 1 (6.2) | 0 | 0.28 |
| *C. glabrata* | 0 (0) | 3 (9.4) | 0.33 |
| *C. krusei* | 0 (0) | 1 (3.1) | 1 |
| Received antifungal therapy, *n* (%) | | | |
| Azoles | 11 (68.8) | 26 (81.2) | 0.46 |
| Candins | 4 (25.0) | 8 (25.0) | 1 |
| Liposomal amphotericin B | 3 (18.8) | 4 (12.5) | 0.67 |
| Combination therapy | 3 (18.8) | 5 (15.6) | 1 |
| Sequential therapy | 4 (25.0) | 6 (32.0) | 0.71 |
| Length of antifungal therapy (days), mean ± SD | 22 ± 11 | 23 ± 19 | 0.75 |
| Adequate antifungal therapy within first 48 h[b] | 11/15 (73.3) | 20/30 (66.7) | 0.74 |
| Adequate control source of infection within first 48 h | 8/11 (72.7) | 12/19 (63.2) | 0.7 |
| Length of hospital stay (days), mean ± SD | 49 ± 29 | 63 ± 22 | 0.08 |
| 1-year mortality rate | 8 (50) | 8 (25) | 0.11 |

[a]The characteristics of the first episode are depicted.
[b]Information was available for 45 patients.

and four by the same species but different genotypes. The presence of clusters (identical genotypes infecting different patients) was excluded because all genotypes found were unique and infected one patient each.

**TABLE 2. Risk factors for recurrent candidaemia: multivariate analysis**

| Variables | OR | 95% CI | p |
|---|---|---|---|
| Male sex | 0.80 | 0.12-5.23 | 0.82 |
| Age | 1.00 | 0.96-1.05 | 0.92 |
| *Candida parapsilosis* | 9.10 | 1.33-62.00 | 0.02 |
| Gastrointestinal underlying disease | 67.16 | 5.23-861.71 | 0.001 |
| Presentation with septic shock | 3.65 | 0.36-36.68 | 0.27 |

As shown in Fig. 2, the distribution of relapses and re-infections could not be associated with time of recurrence (3.7 months versus 3.9 months). Both relapses and re-infections could occur from 1 month to 34.4 months after the first episode. Among the five episodes occurring during the first 3 months, three corresponded to re-infections associated with endovascular catheters and the other two to relapses due to septic thrombophlebitis. Episodes detected after 3 months could be again either re-infections (mainly of intra-abdominal origin) or relapses of different origins.

Patients with relapses had more underlying cardiovascular conditions (83.3% versus 12.5%, p 0.03) and more intravascular infections (83.3% versus 37.5%, p 0.14), whereas patients with re-infections had more malignancies (0 versus 62.5%, p 0.03) or intra-abdominal disease (Table 3). These latter patients usually experienced a second episode of candidaemia after the introduction or re-establishment of risk factors such as new abdominal surgery, systemic chemotherapy, or corticosteroid therapy (Table 3).

## Discussion

Our findings suggest that approximately 1.5% of patients with candidaemia may develop a late recurrence more than 1 month after the apparent cure of the initial episode and that these LR episodes are more common in patients with underlying gastrointestinal diseases and in patients with *C. parapsilosis* fungaemia. About half of all episodes of LR candidaemia are relapses and the other half are re-infections. Relapses are mainly associated with intravascular complications, such as endocarditis and thrombophlebitis, whereas re-infections are mainly associated with catheters or with intra-abdominal infections in patients with cancer.

Medical literature contains few series of recurrent episodes of BSI (second episode of BSI caused by microorganisms of the same genus and species) [1,2,25]. The incidence of recurrent BSI due to specific bacteria such as *Streptococcus pneumoniae* [6,10], *Enterococcus* spp. [7], *Staphylococcus aureus* [8,11], or *Escherichia coli* [9] ranges from 2.1% to 13.3% and is usually

**TABLE 3. Patients with late recurrent candidaemia: characteristics, treatment and outcome**

| | First episode | | | | | | | | Second episode | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age (yr)/ sex | Underlying condition | *Candida* spp. | Source/Final diagnosis | Prosthetic devices | TEE | Therapy | Discharged | Days until recurrence | Acquisition | *Candida* spp | Source/type of infection | Therapy | Outcome | Classification /genotype |
| [1] 0/F | Prematurity, necrotizing enterocolitis and patent ductus arteriosus, abdominal surgery | *C. albicans* | Catheter-related | Catheter and ventriculo-peritoneal shunt | Negative | AmB 21 days, catheter withdrawal | No | 96 | Nosocomial | *C. albicans* | Catheter-related | AmB for 5 days and CVC withdrawal | Died at +5 days | Relapse/ same genotype |
| [2] 12/M | Klippel–Feil syndrome and Sprengel's deformity, surgery for scoliosis, CRRT | *C. parapsilosis* | Catheter-related | Catheters | Negative | AmB 6 days. After fluconazole 14 days, catheter withdrawal | No | 31 | Nosocomial | *C. parapsilosis* | Thrombophlebitis | Fluconazole for 21 days | Cured | Relapse/ same genotype |
| [3] 56/F | CHF, ostium primum defect, cardiac surgery, CRRT | *C. albicans* | Catheter-related/ ocular candidiasis | Catheters, tracheostomy, pericardial Goretex patch | Negative | Fluconazole 28 days, CVC withdrawal | No | 49 | Nosocomial | *C. albicans* | Thrombophlebitis | Fluconazole for 4 weeks | Cured | Relapse/ same genotype |
| [4] 60/M | Aortic and mitral valve replacement and ascending aortic Dacron graft, corticosteroid therapy | *C. parapsilosis* | Primary | Aortic endoprosthesis, prosthetic heart valves, abdominal mesh | Negative | AmB + fluconazole 21 days | Yes | 388 | Community-acquired | *C. parapsilosis* | Prosthetic aortic valve endocarditis | No antifungal therapy was initiated | Died at +7 days | Relapse/ same genotype |
| [5] 70/M | Heart valve disease | *C. parapsilosis* | Catheter-related | Prosthetic mitral valve | Negative | Fluconazole 13 days followed by caspofungin for 22 days, CVC withdrawal | Yes | 143 | Healthcare-associated | *C. parapsilosis* | Prosthetic mitral valve endocarditis | AmB for 14 days followed by lifelong-term suppressive therapy with fluconazole | Cured | Relapse/ same genotype |
| [6] 77/M | Aortic aneurism, ileo-femoral by-pass, urinary tract obstruction | *C. albicans* | Urinary | Ileo-femoral bypass | Not performed | Fluconazole 14 days, placement of urethral catheter to resolve urinary tract obstruction | Yes | 1034 | Community-acquired | *C. albicans* | Urinary | Fluconazole for 24 days | Died at +30 days | Relapse/ same genotype |
| [7] 0/M | Prematurity, gastroschisis, intestinal surgery. multiple cerebral stroke, TPN | *C. parapsilosis* | Abdominal | Catheters | Not performed | AmB 20 days, abdominal surgery (necrotic tissue resection) | No | 114 | Nosocomial | *C. parapsilosis* | Abdominal | AmB for 18 days | Cured | Re-infection/ different genotype |
| [8] 4/M | Down syndrome, tracheo-oesophageal fistula, Nissen fundoplication, TPN | *C. parapsilosis* | Catheter-related | Catheter. Tracheal prosthesis | Negative | AmB 8 days followed by caspofungin 7 days and fluconazole 21 days, catheter withdrawal | No | 112 | Nosocomial | *C. albicans* | Primary | Fluconazole for 14 days | Cured | Re-infection/ different species |

***Continued***

**TABLE 3. Continued**

| | First episode | | | | | | | | Second episode | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age (yr)/ sex** | **Underlying condition** | ***Candida* spp.** | **Source/Final diagnosis** | **Prosthetic devices** | **TEE** | **Therapy** | **Discharged** | **Days until recurrence** | **Acquisition** | ***Candida* spp** | **Source/type of infection** | **Therapy** | **Outcome** | **Classification /genotype** |
| [9] 49/F | Gastric cancer with peritoneal carcinomatosis, chemotherapy | *C. parapsilosis* | Abdominal/ocular candidiasis | None | Negative | Caspofungin 14 days | Yes | 168 | Nosocomial | *C. parapsilosis* | Abdominal | Fluconazole for 28 days | Cured | Re-infection/ Different genotype |
| [10] 54/F | Ovarian cancer with pleural metastasis, peritoneal carcinomatosis, TPN | *C. parapsilosis* | Catheter-related | Catheter | Negative | Fluconazole 14 days, catheter withdrawal | Yes | 169 | Nosocomial | *C. parapsilosis* | Abdominal | No antifungal therapy was administered because the patient had a terminal disease | Died at +6 days | Re-infection/ different genotype |
| [11] 54/F | Gastric cancer with peritoneal carcinomatosis, chemotherapy, TPN and recent abdominal surgery | *C. albicans* | Catheter-related | Catheter | Negative | Caspofungin 4 days followed by fluconazole 28 days, catheter withdrawal | No | 30 | Nosocomial | *C. glabrata* | Catheter-related | Micafungin for 14 days, catheter withdrawal | Cured | Re-infection/ different species |
| [12] 68/M | Lung cancer | *C. parapsilosis* | Catheter-related | Catheter | Not performed | Fluconazole 5 days, catheter withdrawal | No | 71 | Nosocomial | *C. tropicalis* | Catheter-related | Caspofungin for 8 days, catheter withdrawal | Died at +8 days | Re-infection/ different species |
| [13] 85/F | Heart valve disease, biological aortic valve replacement, probable invasive pulmonary aspergillosis | *C. tropicalis* | Catheter-related | Catheter | Negative | Caspofungin and voriconazole combination therapy 42 days, catheter withdrawal | No | 32 | Nosocomial | *C. glabrata* | Catheter-related | Caspofungin for 14 days, catheter withdrawal | Died at +11 days | Re-infection/ different species |
| [14] 79 /M | Colorectal cancer, TPN | *C. albicans* | Catheter-related | Catheter | Negative | Fluconazole 20 days, catheter withdrawal | Yes | 817 | Healthcare-associated | *C. albicans* | Urinary | Fluconazole for 20 days, nephrostomy for ureteral obstruction | Cured | Re-infection/ different genotype |
| [15] 72/M | Colorectal cancer with hepatic metastasis, TPN | *C. tropicalis* | Abdominal/ tertiary peritonitis | Abdominal mesh | Not performed | Fluconazole 15 days, surgical drainage of infection | Yes | 233 | Healthcare-associated | *C. tropicalis* | Native tricuspid valve endocarditis | Fluconazole for 20 days, tricuspid valve replacement | Died at +20 days | Unknown |
| [16] 45/M | Wide intestinal resection and hemi-colectomy for intestinal necrosis, TPN | *C. orthopsilosis* | Catheter-related | Catheter | Negative | AMB 10 days followed by fluconazole 33 days, catheter withdrawal | Yes | 81 | Community-acquired | *C. orthopsilosis* | Aortic valve endocarditis | Antifungal treatment not performed | Died at +4 days | Unknown |

AMB, amphotericin B; CHF, coronary heart failure; CRRT, continuous renal replacement therapy; CVC, central venous catheter; TEE, transesophageal echocardiography; TPN, total parenteral nutrition.

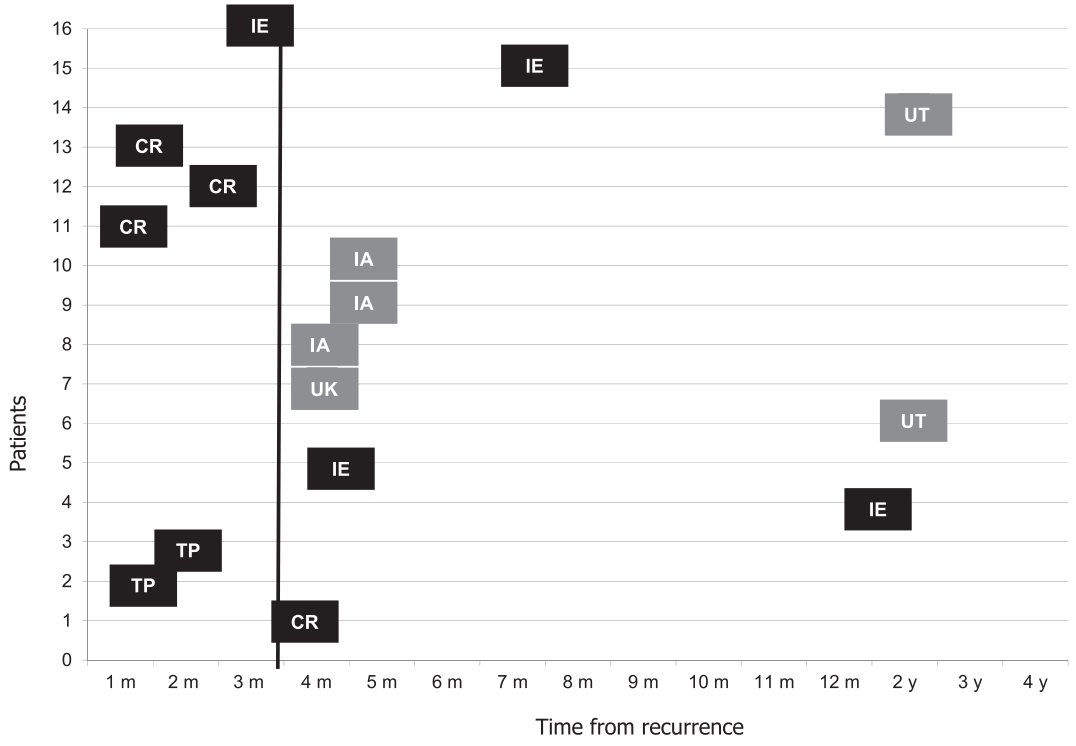


**FIG. 1.** Endovascular and non-endovascular origin of infection according to time to recurrence of second episode of late recurrent candidaemia. Endovascular foci are shown with black squares, non-endovascular foci with grey squares. CR, catheter-related bloodstream infection; IA, intra-abdominal origin; IE, infective endocarditis; TP, thrombophlebitis; UK, unknown origin; UT, urinary tract.

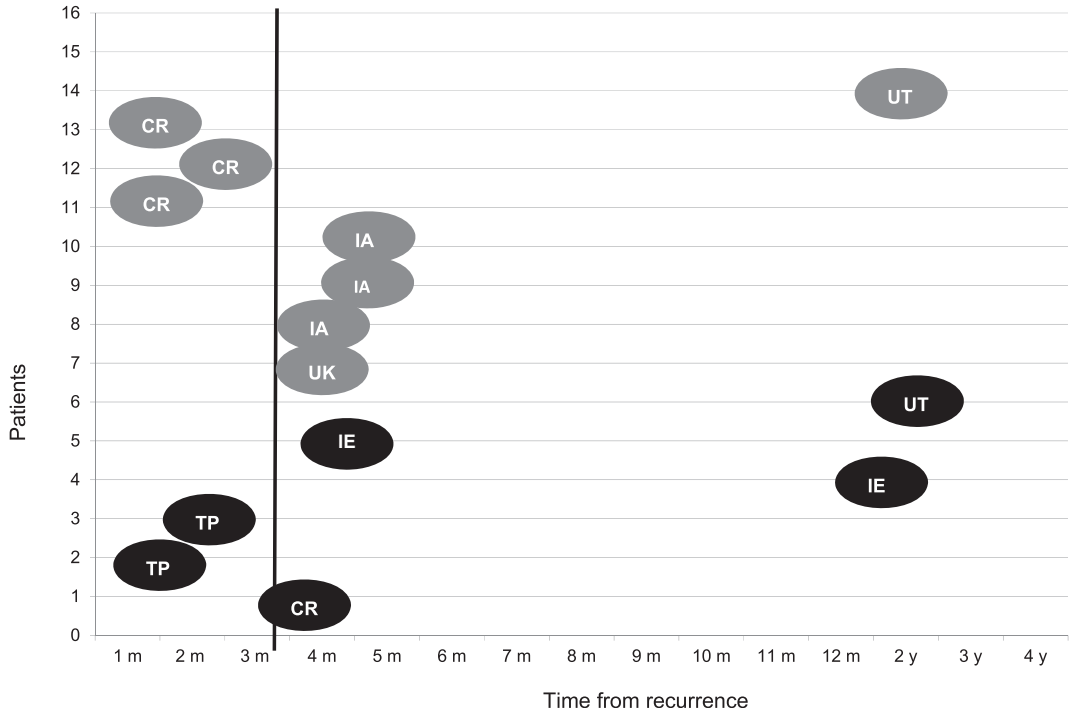


**FIG. 2.** Time to recurrence and origins of second episodes of candidaemia. Comparison of re-infections and relapses. Relapses are shown with a black circle, re-infections with a grey circle. Genotyping analysis was performed for 14 of 16 patients. CR, catheter-related bloodstream infection; IA, intra-abdominal origin; IE, infective endocarditis; TP, thrombophlebitis; UK, unknown origin; UT, urinary tract.

linked to a specific underlying disease, mucositis, source of BSI, or inadequate antibiotic treatment.

From a clinical point of view, it is important to understand the differences between persistent [26] or LR [13–17,19] candidaemia. Persistent candidaemia consists of the maintenance of positive blood cultures or early reappearance of fungaemia (<1 month). It is usually the expression of therapeutic failure related to host factors [27], indwelling central venous catheters [28], or drug resistance [29]. On the other hand, LR candidaemias are defined by most authors [13,14,17,19], as those that occur more than 30 days apart in a patient previously cured. Their clinical significance remains a matter of debate.

However, the article that includes the larger population of patients with LR candidaemia ($n$ = 9) [13] used different criteria, including as LR not only those episodes occurring at least 30 days after the last positive blood cultures, but also all earlier second episodes caused by different species of *Candida*. With this definition the authors reported an incidence of 4.4% [13], which is higher than that reported in our study (1.5%) with the more restricted criteria.

Patients with LR candidaemia usually have several underlying conditions [13,17]. Asmundsdottir *et al.* [13] found a significant association between LR candidaemia and gastrointestinal disease. In their study, including nine patients, more than half of the cases had an underlying gastrointestinal disease compared with 18.5% of the 298 patients who did not experience recurrence. In our case–control study, an underlying gastrointestinal disease (mainly tumours, intestinal necrosis, or inflammatory bowel disease) was also an independent risk factor for LR candidaemia (56.2% versus 3.1%). The gastrointestinal tract is a frequent site of *Candida* colonization [30] and is the main origin of candidaemia in some studies [31]. We hypothesized that these patients were probably heavily colonized by *Candida* spp. and developed fungaemia when they had a gastrointestinal barrier disruption that occurred in circumstances such as chemotherapy, bowel perforation and abdominal surgery [17].

We found a higher probability of recurrence among patients with fungaemia due to *C. parapsilosis*. Compared with other species, *C. parapsilosis* is typically associated with the ability to form biofilms on implanted devices [32–35], suggesting that this yeast could be associated with a late episode of recurrence caused by intravascular clots or formation of biofilm on prosthetic devices. Indeed, we observed a high number of intravascular complications such as thrombophlebitis and endocarditis as the clinical presentation of LR candidaemia (10 out of 16 patients, 62.5%), suggesting a suppressive—but not curative—role for antifungal drugs during the initial episode. Ours is the first study to show this association. Asmundsdottir *et al.* [13] did not find a link between *Candida* species and LR candidaemia, probably because of the low proportion of *C. parapsilosis* in their study. These findings may point to potential differences in the epidemiology of candidaemia between northern and southern Europe.

Overall, 42.9% of LR episodes were relapses caused by the same original strain. Contrary to what was expected, the interval between episodes was surprisingly extended and did not help us to differentiate relapses from re-infections [13,17]. However, we observed a clear pattern of distribution of clinical manifestations over time. If LR candidaemia occurred within 3 months of the first episode, then the clinical source of the infection was in most cases a central venous catheter, an endocarditis or a suppurative thrombophlebitis, independently of the type of recurrence (relapse or re-infection). On the other hand, LR candidaemias occurring after 3 months suggested a wider possibility of diagnosis, mainly intra-abdominal infection, infective endocarditis or urinary tract infection.

Despite it not reaching statistical significance, the 1-year mortality rate observed in patients with LR episodes was higher than in patients with a single episode of candidaemia (8/16 patients, 50% versus 8/32 patients 25%, p 0.11). The high mortality associated with LR candidaemia probably reflects the severity of the underlying diseases. Indeed, the majority of our patients had at least one severe underlying condition such as neoplasia or cardiovascular disease requiring surgery.

Our study is subject to a series of limitations, in particular, its retrospective nature. Prospective studies of the incidence and risk factors of recurrent candidaemia are lacking. Our analysis is the largest to date (>1200 episodes). Second, although the patients were evenly distributed throughout the study period, the timeframe is long and includes a number of changes in patient management that may indirectly impact on the results. Third, the reported incidence of LR candidaemia could be understated, as some patients could have been treated in other hospital settings.

In conclusion, we show that LR candidaemia is a relatively rare event associated with a high mortality rate. Patients with an initial episode of candidaemia due to *C. parapsilosis* and underlying gastrointestinal disease are significantly more likely to present a recurrent episode.

## Acknowledgements

We would like to acknowledge Carlos Sanchez for helping us with the elaboration of the database and Teresa Peláez for permitting us to genotype clinical strains of *Candida* that she stored over the years. We would also like to acknowledge Leopoldo Córdova for helping us with data compilation.

## Transparency Declaration

Nothing to declare.

## Funding

This study was partially financed by the PROgrama MULti-disciplinar para la Gestión de Antifúngicos y la Reducción de Candidiasis Invasora (PROMULGA) II Project, Instituto de Salud Carlos III (grant number PI13/01148)

## Appendix 1. Description of six patients with late relapsing candidaemia

**Patient 1** was a premature girl with two episodes of *C. albicans* candidaemia 4 months apart. In both cases, the patient had catheter-related candidaemia; however, we cannot rule out an intravascular complication, since an aggressive diagnostic work up was not performed owing to the patient's poor clinical condition.

**Patient 2** was a 12-year-old boy with Kippel–Feil syndrome and Sprengel's deformity who developed acute renal failure after surgery to treat scoliosis. He had two episodes of *C. parapsilosis* candidaemia 31 days apart. The initial episode was considered to be associated with a CVC in the femoral vein that was removed 3 days after blood cultures were drawn and tip culture was positive for *C. parapsilosis*. An ultrasound scan of the femoral vein revealed deep thrombosis. The patient was treated with amphotericin B for 6 days followed by fluconazole for 14 days. Candidaemia recurred 31 days later and the source was considered to be the infected clot. The patient received 21 days of intravenous fluconazole, and there were no further recurrences of candidaemia.

**Patient 3** was a 56-year-old woman who underwent cardiac surgery for ostium primum defect. During the post-operative period, she also presented renal insufficiency requiring haemodialysis. Her first episode of *C. albicans* catheter-related candidaemia was treated with 28 days of fluconazole and with removal of her catheter from the subclavian vein. A new episode occurred after 49 days, with a clot at the site of the previous catheter. Fluconazole was administered for 4 weeks with a good clinical outcome.

**Patient 4** was a 60-year-old man who had undergone aortic and mitral valve replacement and had two episodes of *C. parapsilosis* candidaemia during a 1-year period. The source of infection during the first episode was unclear, because he had no CVC, and an echocardiogram was negative for endocarditis. He was treated with amphotericin B and fluconazole for 3 weeks, resulting in clearance of candidaemia and clinical improvement. He was readmitted with septic shock after 1 year and died. An echocardiogram close to the time of death revealed a vegetation on his prosthetic aortic valve, whereas blood cultures before death revealed growth of *C. parapsilosis*. Both isolates were genotypically identical.

**Patient 5** was a 70-year-old man who underwent prosthetic mitral valve replacement. On day 60 after surgery, a first episode of catheter-related candidaemia became complicated with suppurated thrombophlebitis. The patient was treated with 35 days of antifungal therapy and catheter withdrawal. He was readmitted after 5 months with a new episode of candidaemia and diagnosis of prosthetic mitral valve endocarditis. He was treated initially with amphotericin B followed by lifelong suppressive therapy with fluconazole. An identical *C. parapsilosis* isolate was recovered in both episodes.

**Patient 6** was a 77-year-old man who was hospitalized for fever and bilateral urinary tract obstruction secondary to ureteral stones. Blood and urine culture yielded *C. albicans*. The patient was treated with placement of ureteral stents and fluconazole (14 days). He was discharged and the ureteral stents were removed a few months later. He had persistent asymptomatic candiduria during the following years, although antifungal therapy was never implemented. Three months after the first episode he was readmitted for transurethral resection of a bladder tumour. On day +5 he had fever with a blood culture that was positive for *C. albicans*, which was also isolated from a urine sample. He was treated with fluconazole for 24 days and died 1 month later. Both blood isolates were identical.

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