Epidemiology, Risk Factors, and Prognosis of *Candida parapsilosis*

Bloodstream Infections: Case-Control Population-Based Surveillance Study of Patients in Barcelona, Spain, from 2002 to 2003

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**Candida parapsilosis** has emerged as an important yeast species causing fungemia. We describe the incidence and epidemiology of *C. parapsilosis* fungemia. Data from active population-based surveillance in Barcelona, Spain, from January 2002 to December 2003 were analyzed. We focused on 78 episodes of *C. parapsilosis* fungemia, and we compared them with 175 *Candida albicans* controls. *C. parapsilosis* accounted for 23% of all fungemias. The annual incidences were 1 episode per 105 patients, 1.2 episodes per 104 discharges, and 1.7 episodes per 105 patient days. All isolates but one (99%) were fluconazole susceptible. Seventy-two isolates (92%) were inpatient candidemias. Forty-two episodes (51%) were considered catheter-related fungemia, 35 (45%) were considered primary fungemia, and 3 (4%) were considered secondary fungemia. Risk factors for candidemia were vascular catheterization (97%), prior antibiotic therapy (91%), parenteral nutrition (54%), prior surgery (46%), prior immunosuppressive therapy (38%), malignancy (27%), prior antifungal infection (26%), transplant recipient (16%), neutropenia (12%), and prior colonization (11%). Multivariate analysis of the differential characteristics showed that the factors that independently predicted the presence of *C. parapsilosis* fungemia were neonate patients (odds ratio [OR], 7.5; 95% confidence interval [CI], 2.1 to 26.8; \( P = 0.002 \)), transplant recipients (OR, 9.2; 95% CI, 1.9 to 43.3; \( P = 0.005 \)), patients with a history of prior antifungal therapy (OR, 5.4; 95% CI, 1.8 to 15.9; \( P = 0.002 \)), and patients who received parenteral nutrition (OR, 2.2; 95% CI, 1.09 to 4.6; \( P = 0.028 \)). The overall mortality rate was lower than that associated with *C. albicans* candidemia (23% versus 43%; \( P < 0.01 \)). In summary, *C. parapsilosis* was responsible for 23% of all candidemias and was more frequent in neonates, in transplant recipients, and in patients who received parenteral nutrition or previous antifungal therapy, mainly fluconazole. The mortality rate was lower than that associated with *C. albicans* fungemia.

The incidence of bloodstream infections caused by *Candida* progressively increased over the past two decades, accounting for 8 to 10% of all nosocomial bloodstream infections (BSI) in the United States during the 1990s (10). Although *Candida albicans* remains the most common fungal isolate from blood, longitudinal studies have detected a trend toward an increased prevalence of other *Candida* spp. (24, 35). Compared with the 1980s, a larger proportion of *Candida BSI* is now caused by *Candida glabrata* in the United States (35) and by *Candida parapsilosis* and *Candida tropicalis* in European, Canadian, and Latin American hospitals (11, 20, 23).

This change in the most frequent cause of candidemia has been explained in part by the high affinity of *C. parapsilosis* for intravascular devices and parenteral nutrition (11, 16, 17, 32, 38) and their widespread use. The increasing use of antifungal agents to prevent infections caused by *Candida* in high-risk patients might also have favored changes in the species causing infections (11). Nosocomial outbreaks of *C. parapsilosis* have also been described previously, and the hands of healthcare workers may be the predominant environmental source (4, 6, 7, 9, 16, 19, 27, 38, 39).

Because of this change and the importance of *C. parapsilosis* in our area, we have focused on *C. parapsilosis* fungemia by analyzing data from active population-based surveillance in Barcelona, Spain (2, 8), to describe its prevalence. We compared all our *C. parapsilosis* fungemia patients with *C. albicans* fungemia patients (controls) in order to identify the risk factors and the clinical characteristics of *C. parapsilosis* fungemia.

**MATERIALS AND METHODS**

Data sources. Prospective population-based surveillance for candidemia was conducted in 14 hospitals in Barcelona (Spain) from 2002 to 2003. Fourteen major institutions participated, ranging in size from 214 to 1,295 beds. Reporting of cases was laboratory based. Each episode of candidemia was reported to the study coordinator (D.R.), who visited the institutions to complete a standardized data collection form. Cases were defined as isolation of *Candida* spp. from the blood of a Barcelona resident. Candidemias that occurred more than 30 days after the initial case were considered new cases. Cases detected either prior to or within 2 days of hospital admission were considered outpatient acquired.

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report here all cases of *C. parapsilosis* fungemia. Cases of candidemia caused simultaneously by different species of *Candida* were excluded from the analysis, as we understand that they constitute a different subgroup of patients.

**Definitions.** Cases occurring in the absence of an apparent portal of entry were classified as primary. A case was considered likely to be catheter related when (i) quantitative culture of the catheter tip yielded more than 15 CFU of a *Candida* species or (ii) simultaneous quantitative cultures of blood samples showed a ratio of ≥5:1 of CFU between blood samples obtained through the catheter and a peripheral vein (31). Secondary candidemias were defined as cases that occurred after a potential source of infection was identified. Such sources could be identified by a positive abdominal or urinary culture. We defined early mortality as death 3 to 7 days after diagnosis and late mortality as death between days 8 and 30.

**Microbiological methods.** Detection of candidemia and species identification of isolates were performed at the participating laboratories according to their standard protocols. Isolates were sent to the Mycology Reference Laboratory (MRL), National Centre for Microbiology, Madrid, Spain, for species confirmation and antifungal susceptibility testing. When the MRL and submitting laboratory identifications differed, final identification by the MRL was used for the purpose of this analysis. MICs of amphotericin B, itraconazole, voriconazole, caspofungin, fluconazole, and 5-flucytosine were determined by the EUCAST broth microdilution method (30). Isolates were classified as susceptible or as showing decreased susceptibility. The latter category included the susceptible dose-dependent, intermediate (relevant to 5-flucytosine), and resistant categories defined by the CLSI (formerly NCCLS) (21).

**Statistical analysis.** Incidence rates were calculated using denominator data obtained from the 2001 local census. Hospital-specific incidences were calculated using denominators from data for the total number of patients discharged and patient days from individual hospitals from 2002 to 2003. Overall incidence was calculated using denominators of summed discharges and patient days to calculate pooled mean rates.

Statistical analysis was performed with the SPSS software package (version 12.0). Categorical variables are expressed as proportions (percentages), and numerical data are expressed as means (±standard deviations), medians, and ranges. Chi-square test or Fisher’s exact test (two-tailed) was used to compare categorical variables, and the unpaired Student’s t-test was used for continuous variables. Stepwise logistic multivariable analysis to identify differential characteristics of *C. parapsilosis* fungemia was carried out. Variables with P values of <0.1 in the univariate analysis were included in the multivariate model. Statistical significance was set at a P value of <0.05.

**RESULTS**

**Prevalence of *C. parapsilosis* fungemia.** Between 2002 and 2003, we detected 341 patients with *Candida* BSI in our prospective population-based surveillance. Four patients had a recurrent episode, resulting in 345 total cases (175 corresponded to *C. albicans*, 78 corresponded to *C. parapsilosis*, 29 corresponded to *C. glabrata*, 34 corresponded to *C. tropicalis*, 12 corresponded to *Candida krusei*, 6 corresponded to polymicrobial candidemia, and 11 corresponded to other *Candida* spp.). Seventy-eight episodes of *C. parapsilosis* fungemia in 76 patients were identified, resulting in 23% (78/345) of all candidemia episodes. The average annual incidence of *C. parapsilosis* fungemia was 1 case per 100,000 inhabitants. Overall, the surveillance period included 647,498 hospital discharges and 4.7 million patient days; the pooled mean rate of bloodstream episodes defined by the CLSI (formerly NCCLS) (21).

**Epidemiology and outcome.** Clinical characteristics of the patients with *C. parapsilosis* fungemia are shown in Table 2. Fifty-five percent of the patients were male, and the median age was 36 years (range, <1 to 80), with 28% of them being less than 1 year old. Among the neonatal population (<3 months), *C. parapsilosis* was the most frequent isolate, accounting for 67% of the cases.

Seventy-three cases (92%) were inpatient candidemias (16 patients admitted in neonatal intensive care units, 15 patients in intensive care units, 11 patients in hematology-oncology departments, 9 patients in pediatric wards, 9 patients in general surgery, and 13 patients in other medical wards), and five (8%) were considered outpatient acquired. With regard to the source of the fungemia, 40 episodes (51%) were considered catheter-related candidemias, 35 episodes (45%) were considered primary candidemias, and 3 episodes (4%) were considered secondary candidemias.

The more frequent risk factors associated with *C. parapsilosis* fungemia were intravenous lines at diagnosis (97% of episodes), prior antibiotic treatment (91%), parenteral nutrition (54%), prior surgery (46%), prior immunosuppressive therapy (38%), malignancy (27%), prior fluconazole treatment (17%), prior amphotericin B treatment (9%) (conventional amphotericin B in 3% and amphotericin B lipid formulations in 6% of cases), transplant recipient (16%), neutropenia (12%), and diabetes mellitus (9%). Prior colonization with *C. parapsilosis* was found in only eight (10%) episodes, with prior positive urine cultures in five cases, positive skin cultures in three cases, gastrointestinal colonization in two cases, and positive tracheal aspirations in two cases (in four episodes, colonization occurred at multiple sites).

Clinically, fever was present in all episodes, 8 (10%) patients developed renal failure, and 17 (22%) patients presented with septic shock. Three patients had echocardiographically documented infective endocarditis, and endophthalmitis was diagnosed in two of them. One case of *C. parapsilosis* meningitis was diagnosed in a preterm neonate treated with parenteral hyperalimentation.

Seventy-one patients (91%) received systemic antifungal therapy for a median length of 17 days (range, 2 to 54 days). Seven patients were not treated with a systemic antifungal agent, and four of them died before blood culture results were available. Therapy consisted of fluconazole in 30 (38%) episodes, amphotericin B (conventional or lipidic formulations) in 24 (31%) episodes, and itraconazole, voriconazole, and caspofungin in one case each. A combination of two antifungal drugs

<table>
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<tr>
<th>Antifungal agent</th>
<th>Range</th>
<th>Geometric mean</th>
<th>90%</th>
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</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>0.03-0.25</td>
<td>0.19</td>
<td>0.25</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>0.125-1</td>
<td>0.15</td>
<td>0.25</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>0.125-64</td>
<td>0.41</td>
<td>1</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.01-0.25</td>
<td>0.02</td>
<td>0.06</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0.01-0.5</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>0.125-2</td>
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was used in eight (10%) episodes, and treatment with two antifungal drugs sequentially was used in six (8%) episodes.

Catheter removal was part of treatment in 67 (86%) of the candidemia episodes. Reasons for not removing the catheter were early death in three cases and effective antifungal therapy without catheter management in three cases. We do not know the status of catheter management for three patients. The overall mortality rate was 23% (18 patients), with early death in three cases and effective antifungal therapy in eight (10%) episodes, and treatment with two antifungal agents in five (6%) episodes. Reasons for not removing the catheter included parental consent in three cases, technical difficulties in two cases, and patient preference in one case.

In order to identify risk factors for and differential clinical characteristics of C. parapsilosis candidemia, we used cases of C. albicans as controls and compared the 78 C. parapsilosis episodes with the 175 C. albicans episodes from the same population-based surveillance. The differences found in the univariate analysis are shown in Table 2. C. parapsilosis was more frequent among neonates (20% for C. parapsilosis versus 4% for C. albicans; P < 0.001) and in patients with intravenous lines (97% versus 86%; P = 0.004). Vascular catheters were the most common source of C. parapsilosis fungemia (51% versus 31%; P = 0.003). Patients with C. parapsilosis fungemia had more often received antifungal agents before the fungemia (26% versus 7%; P < 0.001), were on parenteral nutrition (54% versus 33%; P = 0.002), and had undergone transplantation more frequently (16% versus 2%; P < 0.01) than patients with C. albicans fungemia. Early and overall mortality rates of C. parapsilosis fungemia were lower than those associated with C. albicans fungemia (6% versus 25% at day 7 and 23% versus 43% for overall mortality; P < 0.01 for both comparisons).

On the other hand, C. albicans was more frequent in the elderly population (54% versus 27%; P < 0.001), in diabetic patients (25% versus 9%; P = 0.002), and in patients previously colonized by the same Candida spp. (42% versus 10%; P < 0.001).

On multivariate analysis, the risk factors significantly associated with C. parapsilosis fungemia compared to those of C. albicans fungemia were neonate patients (odds ratio [OR], 7.5; 95% confidence interval [CI], 2.1 to 26.8; P = 0.002), transplant recipients (OR, 9.2; 95% CI, 1.9 to 43.3; P = 0.005), prior antifungal therapy (OR, 5.4; 95% CI, 1.8 to 15.9; P = 0.002), and parenteral nutrition received (OR, 2.2; 95% CI, 1.09 to 4.6; P = 0.028). Previous colonization by the same species of Candida (OR, 0.09; 95% CI, 0.03 to 0.26; P < 0.001) and early mortality (OR, 0.23; 95% CI, 0.07 to 0.72; P = 0.012) were significantly less frequent in C. parapsilosis fungemia than in C. albicans fungemia.

### DISCUSSION

The overall incidence of C. parapsilosis fungemia in Barcelona is lower than that in the United States (1 case per 100,000 people versus 1.3 cases per 100,000 people, respectively) (12) but is higher than that found in a recent report from Finland (0.3 cases per 100,000 people) (26). C. parapsilosis rates among hospitalized patients in this study (1.7 episodes per 100,000 patient days) were lower than reported incidence rates from the United States (2 episodes per 100,000 patient days) (12) but higher or similar to previously reported C. parapsilosis fungemia rates for other European countries. These have ranged from 0.05 episodes per 100,000 patient days in Swiss hospitals in 2000 (20) to 0.2 episodes per 100,000 patient days in Norway in 1996 (34), 0.7 episodes per 100,000 patient days in The Netherlands in 1995 (36), and 0.8 episodes per 100,000 patient days in France in 1995 (28).

The prevalence of C. parapsilosis fungemia has changed over the years, and now, in some areas, C. parapsilosis is the second most common species found in patients with candidemia (2, 8, 23, 32). The reasons for the rising incidence of C. parapsilosis candidemia are not completely known, although indwelling venous catheters and parenteral nutrition have been recognized as specific risk factors (1, 7, 11, 16, 17, 18, 37, 38). Most experimental studies have indicated that the adherence of C. parapsilosis to acrylic is greater than that of C. albicans (11, 38).

The affinity of C. parapsilosis for foreign material is proved by infections related to peritoneal dialysis catheters (14) and prosthetic heart valves (9), possibly linked to the fact that adhesion (16, 38) and biofilm formation (6, 15) are especially important for C. parapsilosis fungemia. C. parapsilosis has been shown to have a selective growth advantage in total parenteral nutrition solutions that promote the adhesion and growth of the yeast (11, 16, 37, 38). Our findings agree with previous epidemiological studies showing that C. parapsilosis infections are more frequent in patients with intravenous lines, with most of them receiving parenteral nutrition (54% for C. parapsilosis infections versus 33% for C. albicans infections; P < 0.01), and frequently, the catheter is the portal of entry (54% versus 31%; P < 0.01).
Our findings confirm the worldwide reports of low or negligible levels of fluconazole resistance in *C. parapsilosis* isolated from blood cultures (23, 24, 25). Nothing suggests that antifungal susceptibility tests should be routinely performed, but correct identification of *Candida* isolates causing bloodstream infections at the species level is therapeutically significant in view of their distinct susceptibility profile.

The clinical conditions of our patients probably represent the overall spectrum of *C. parapsilosis* candidemia better than series from a single center or an outbreak. When we compared patients with *C. parapsilosis* infection to those with *C. albicans* infections, the former patients are younger (20% for *C. parapsilosis* infection versus 4% for *C. albicans* infection among neonates, while incidence among elderly people is 27% versus 54%; *P < 0.001*), had more commonly received previous antifungal treatment (26% versus 7%; *P < 0.001*), and had received a transplant (16% versus 2%; *P < 0.001*). Other authors have previously described the predominance of *C. parapsilosis* in children (1, 2, 10, 18, 22). Although these observations remain unexplained, some investigations have suggested that the prevalence of *C. parapsilosis* in children may reflect the aggressive use of intravascular devices to treat neonates (22).

The prevalences of *C. parapsilosis* fungemia in neonates varied greatly, from less than 10% in small series in the 1980s and early 1990s to around 50 to 60% in more recent series (5, 29).

Whereas infections caused by *C. albicans* frequently arise from endogenous sources (frequently colonizing the gastrointestinal and genital mucosae), BSIs caused by *C. parapsilosis* are not generally associated with prior colonization. *C. parapsilosis* is often linked to an exogenous source (hands of healthcare providers) or can be part of the normal flora of the human skin, appearing to be directly introduced into the bloodstream (4, 6, 7, 11, 27, 38). Exceptions to this are infants of very low birth weight in a neonatal intensive care unit, where 5% of infants could be colonized with *C. parapsilosis*, representing 18% of all colonizing strains of *Candida* species. In the neonatal population, the prevalence of *C. parapsilosis* colonization has been described to be inversely proportional to birth weight (3, 33). In our series, 2 out of 16 (12%) neonates were previously colonized by *C. parapsilosis*. It represents a higher proportion of *C. parapsilosis* colonization than has been previously described, although we do not have enough patients to make any conclusion.

A lower mortality rate associated with *C. parapsilosis* fungemia than that associated with bloodstream infection due to other *Candida* species has been confirmed in several previous studies (2, 13, 18, 22, 38). According to this, our data show a lower overall and early mortality in *C. parapsilosis* candidemia compared to *C. albicans* (23% versus 43% overall and 6% versus 25% at day 7, respectively; *P < 0.01*). Late mortality did not significantly differ (17% versus 24%; *P = 0.29*), perhaps due to the role of underlying diseases.

In conclusion, the results of this population-based surveillance study indicate that *C. parapsilosis* isolates constitute 23% of all fungemias in Barcelona, Spain. Risk factors associated with *C. parapsilosis* fungemia, compared with those of *C. albicans*, were neonate patients, transplant recipients, patients who received prior antifungal therapy, and patients who received parenteral nutrition. The majority of isolates were fluconazole susceptible; therefore, this antifungal drug is a reasonable alternative for treatment of *C. parapsilosis* fungemia. Early mortality related with *C. parapsilosis* fungemia remains low.

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