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Candida parapsilosis, an Emerging Fungal Pathogen

David Trofa,[1] Attila Gácser,[2] and Joshua D. Nosanchuk[1]*

Department of Medicine (Division of Infectious Diseases) & Microbiology and Immunology, Albert Einstein College of Medicine of Yeshiva University, Bronx, New York,[1] and Department of Microbiology, University of Szeged, Szeged, Hungary[2]

INTRODUCTION

Since the 1980s, fungi have emerged as major causes of human disease, particularly among immunocompromised individuals and hospitalized patients with serious underlying conditions (210). In fact, since 1979 the annual incidence of fungal sepsis in the United States has increased over 200% (169). *Candida* species are presently the fourth leading cause of nosocomial bloodstream infection in the United States, being responsible for 8 to 15% of all such hospital-acquired infections (292). The total annual burden of candidemias (invasive disease) in the United States is as high as 42,000 infections (29 infections per 100,000 population per year or 24 per 10,000 discharges) (210). Invasive fungal infections result in substantial morbidity and mortality (0.4 deaths per 100,000 population). Hence, these diseases have a significant impact on public health.

Over the past decade, the incidence of *Candida parapsilosis* has dramatically increased. In fact, reports indicate that *C. parapsilosis* is often the second most commonly isolated *Candida* species from blood cultures (5, 34, 51, 52, 54, 90, 144, 177, 213, 215, 231), and *C. parapsilosis* even outranks *Candida albicans* in some European (213), Asian (186, 189), and South American (174) hospitals.

C. parapsilosis was first isolated by Ashford (as a species of *Monilia* that was incapable of fermenting maltose) from the stool of a patient with diarrhea in Puerto Rico in 1928 (12, 286). The species was named *Monilia parapsilosis* to distinguish it from the more common isolate, *Monilia psilosis*, better known today as *Candida albicans*. Although initially considered nonpathogenic, *C. parapsilosis* was identified as the causative agent of a fatal case of endocarditis in an intravenous drug user in 1940 (125). Even at this early point, investigators associated infection with exogenous introduction of *C. parapsilosis*, which astutely foreshadowed the linkage of *C. parapsilosis* with invasive medical instrumentation and hyperalimentation solutions.

Prior to 2005, *C. parapsilosis* was separated into three groups, I to III. However, further genetic studies revealed sufficient differences that have led to the separation of the groups into closely related, distinct species: *C. parapsilosis*, *Candida orthopsilosis*, and *Candida metapsilosis* (267). Nevertheless, *C. parapsilosis* is responsible for the vast majority of clinical disease, and few medical microbiology laboratories distinguish between these species, especially since commercial systems are not sufficient to differentiate between them. Fur-

* Corresponding author. Mailing address: Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461. Phone: (718) 430-3659. Fax: (718) 430-8968. E-mail: nosanchu@aecom.yu.edu.

thermore, few studies in the literature have made this discrimination, although it is hoped that future critical studies will consider the species separately.

C. parapsilosis cells display oval, round, or cylindrical shapes. When grown on Sabouraud dextrose agar, colonies of *C. parapsilosis* are white, creamy, shiny, and smooth or wrinkled. Unlike *C. albicans* and *C. tropicalis*, which can exist in multiple morphogenetic forms, *C. parapsilosis* does not form true hyphae and exists in either a yeast phase or a pseudohyphal form. Pseudohyphae have been observed on cornmeal agar and can be identified by light microscopy (150). Recent evidence shows that *C. parapsilosis* pseudohypha formation is linked to a specific set of amino acids, particularly citrulline, which cause significant changes to cellular and colony morphology (136). Colony phenotypes also depend upon the form of *C. parapsilosis*: yeast colonies exhibit smooth or crater phenotypes, while pseudohyphae exhibit crepe or concentric phenotypes (150).

C. parapsilosis is typically a commensal of human skin, and its pathogenicity is limited by intact integument. *C. parapsilosis* is notorious for its capacity to grow in total parenteral nutrition and to form biofilms on catheters and other implanted devices, for nosocomial spread by hand carriage, and for persistence in the hospital environment (47). *C. parapsilosis* is of special concern in critically ill neonates, causing more than one-quarter of all invasive fungal infections in low-birth-weight infants in the United Kingdom (49) and up to one-third of neonatal *Candida* bloodstream infections in North America (90). Additionally, it is the predominant fungal organism isolated in many neonatal intensive care units (NICUs), where it is often associated with neonatal mortality (26, 49, 232).

Since the 1980s, there has been a marked increase in bloodstream infections due to non-*C. albicans Candida* species, especially *C. glabrata* in the United States and *C. parapsilosis* and *C. tropicalis* in Europe, Canada, and Latin America (5). Although *C. parapsilosis* is often considered less virulent than *C. albicans*, it is the *Candida* species with the largest increase in incidence since 1990. Given the continued emergence of *C. parapsilosis*, we have undertaken a comprehensive review of the literature describing the epidemiology, virulence traits, clinical manifestations, genetics, and antimicrobial susceptibility of *C. parapsilosis* to provide a broad and up-to-date reference for this pathogen.

PREVALENCE

In comparison to other *Candida* species, *C. parapsilosis* has an extensive distribution in nature. Unlike *C. albicans* and *C. tropicalis*, *C. parapsilosis* is not an obligate human pathogen, having been isolated from nonhuman sources (286) such as domestic animals, insects, soil, and marine environments (82). *C. parapsilosis* is also a normal human commensal, and it is one of the fungi most frequently isolated from the subungal space of human hands. Its transient colonization of human integument is the basis of much debate as to whether or not *C. parapsilosis* is a pathogen or bystander in certain infections (see Clinical Manifestations below).

C. parapsilosis isolation is on the rise worldwide. In data from the 2003 SENTRY Antimicrobial Surveillance Program, *C. parapsilosis* was the second most common *Candida* species isolated from normally sterile body sites of hospitalized patients. It accounted for 15.5% of *Candida* isolates in North America, 16.3% in Europe, and 23.4% in Latin America, outranked only by *C. albicans* (51.5%, 47.8%, and 36.5%, respectively) and by *C. glabrata* (21.3%) in North America (177). In contrast, of the 196,508 isolates of *Candida* species considered pathogens from all body sites, obtained from 134 medical centers in the Asia-Pacific region, Latin America, Europe, the Africa-Middle East region, and North America between 1997 and 2005, *C. parapsilosis* accounted for only 6.1% of all isolates, following *C. albicans* (65.6%), *C. glabrata* (11.1%), and *C. tropicalis* (6.9%) (212). However, the incidence of *C. parapsilosis* rose from 4.8% between 1997 and 2000 to 6.6% between 2001 and 2005. Higher rates of *C. parapsilosis* isolation were obtained in a study involving 5,346 clinical *Candida* isolates from 91 medical centers between 2001 and 2006, where it accounted for significant percentages of *Candida* species in the Asia-Pacific regions (15.97%), Latin America (18.62%), Europe (10.63%), and North America (14.04%) (208). Among 840 patients with invasive candidiasis identified at three hospitals affiliated with the Baylor College of Medicine in the United States from September to November 2001, 73.2% patient isolates were *C. albicans* while *C. parapsilosis* accounted for only 4.2%. However, *C. parapsilosis* was isolated proportionally more from blood and indwelling medical devices (34.3%) than was *C. albicans* (8.5%) (140). Hence the incidence of invasive *C. parapsilosis* disease varies geographically and, as described below, is significantly affected by the underlying clinical status of the patients.

RISK FACTORS

Invasive disease with *C. albicans* and *C. tropicalis* is normally preceded by prior colonization, and these fungi are transmitted vertically, typically from mother to child around the time of birth. In contrast, invasive disease caused by *C. parapsilosis* can occur without prior colonization and is frequently transmitted horizontally via contaminated external sources such as medical devices or fluids, the hands of health care workers, prosthetic devices, and catheters.

The increase in the frequency of *C. parapsilosis* infections has been attributed to a variety of risk factors, including the organism's selective growth capabilities in hyperalimentation solutions and its affinity for intravascular devices and prosthetic materials. Immunocompromised individuals such as AIDS patients and surgical patients, particularly those having surgery of the gastrointestinal tract, are at high risk for infection with *C. parapsilosis.* Additionally, patients requiring prolonged use of a central venous catheter or indwelling device, such as cancer patients, are at increased risk for infection with *C. parapsilosis*. For example, a 9-year study of fungemia in leukemia patients at an Italian university hospital reported a total of 79 cases in 77 patients, among which *C. parapsilosis* caused 16 episodes (20.3%) and *C. parapsilosis* was associated more frequently with the presence of a central venous line and the use of parenteral nutrition than any other fungal species (171). In patients with solid tumors and candidemia at the University of Texas M.D. Anderson Cancer Center between 1998 and 2002, the rates of candidemia caused by *C. albicans* and *C. parapsilosis* were 40% and 35%, respectively (270). In contrast, an earlier survey study indicated that *C. parapsilosis*

accounted for only 7% of *Candida* infections in oncology patients (291). Prolonged used of an intravenous catheter for antibiotic administration has also been associated with *C. parapsilosis*. For example, a 30-year-old woman receiving protracted treatment with antibiotics for Lyme disease developed *C. parapsilosis* sepsis, and postmortem examination found that the tricuspid valve orifice was acutely obstructed by a large infected thrombus at the end of the indwelling catheter (207).

Recently, an increasing number of publications have described populations with increased incidences of *C. parapsilosis* disease and have attributed various risks as predisposing factors for infection. There are many differences in the results reported in these publications, as the populations, the numbers of patients included, and the geographical locations of the hospitals are widely diverse. A recent study of 72 patients in Barcelona, Spain, with invasive *C. parapsilosis* identified risk factors that included vascular catheterization (97%), prior antibiotic therapy (91%), parenteral nutrition (54%), prior surgery (46%), prior immunosuppressive therapy (38%), malignancy (27%), transplant receipt (16%), neutropenia (12%), and prior colonization (11%) (5). In a report of 64 episodes of *C. parapsilosis* candidemia from four tertiary care hospitals in São Paulo, Brazil, between 2002 and 2003, the primary risk factors were neutropenia, tunneled central venous catheter, and cancer chemotherapy (34). In other studies, infection with *C. parapsilosis* has been especially associated with hyperalimentation solutions/parenteral nutrition (103, 155, 156, 165, 261, 286), intravascular pressure monitoring devices (286), ophthalmic irrigating solutions (286), antibiotic use (103, 243), prematurity (156, 247), and central venous catheter use (103, 155, 156, 165). Parenteral nutrition in particular facilitates *C. parapsilosis* disease, since the yeast possesses a selective growth advantage in hyperalimentation solutions with high concentrations of glucose (261, 287). Further, studies of total parenteral nutrition show that it can increase the dry weight of biofilms, an important virulence factor of the pathogen, by up to 40% (147).

The population at greatest risk for nosocomial infection with *C. parapsilosis* is that of very and extremely low-birth-weight neonates. Colonization of the skin or gastrointestinal tract is a frequent first step in the pathogenesis of invasive candidal disease, and neonates are especially prone to disease given their compromised skin integrity, susceptibility to gastrointestinal tract infection, long-term need for central venous catheters, and prolonged endotracheal intubation (27). In fact, *C. parapsilosis* can be isolated from approximately one-third of neonates with gastrointestinal colonization by *Candida* species (240) and from the oropharynges of 23% of healthy neonates (53). While the rate of colonization and its significance for pathogenesis are not yet entirely clear, studies have been made relating the two. For instance, a 1994 report on 82 neonates at the George Washington University Hospital in the United States found that 19% of the infants were colonized with *Candida* species. Among those colonized, four developed fungal sepsis due to *C. parapsilosis* and one infant had congenital *C. albicans* sepsis (252). Vertical transmission often results in colonization of *Candida* species from mother to child; however, colonization in infants with *C. parapsilosis* cannot be accounted for by maternal isolates (25, 283). This is not surprising, as *C. parapsilosis* is an infrequent isolate from the vagina (see "Vulvovaginitis" below), thus minimizing exposure of the infant during birth.

The hands of health care workers are major vectors in the exogenous acquisition of *C. parapsilosis*. As a normal commensal of human skin, *C. parapsilosis* poses a major threat to patients interacting with colonized health care workers, particularly when breaches in standard hand-washing protocols occur. Although percentages vary among studies, multiple reports reference *C. parapsilosis* as the yeast organism most commonly isolated from health care workers' hands. In a 1993 to 1995 study of NICU health care workers in the United States, 2,989 cultures were obtained from employees' hands, and 19% were positive for *C. parapsilosis* (240). Further, a 2005 article reported that among 21 NICU workers at the Maringá Regional University Hospital of Praná, Brazil, 13 (62%) were positive for type of yeast, and of those, 7 (53.8%) were *C. parapsilosis* (28).

Molecular typing methods have illustrated the link between hand carriage of *C. parapsilosis* and the horizontal transmission and outbreak of infections of *C. parapsilosis* in hospital environments by showing the genetic similarities among health care workers' and clinical isolates (277). For example, the isolate from a neonate with *C. parapsilosis* candidemia in Pisa, Italy, was genetically indistinguishable from those recovered from the hands of two nurses who had previously handled the newborn (164). In an investigation of a cluster of *C. parapsilosis* infections involving six patients in a Brazilian cancer ward, *C. parapsilosis* was found on the hands of three health care workers, and two isolates were molecularly identical to the outbreak strain (155). Over the course of 55 months, 58 Finnish NICU patients developed serious infections with *C. parapsilosis*, which were attributed to cross-infection during contact between the patients and health care providers (247). Another study of an outbreak infection involving 22 patients in a U.S. community hospital found that the hands of 28% of 19 health care workers, including 14 nurses, 3 physicians, and 2 others, were colonized with *C. parapsilosis*, and one hand isolate was highly related to the outbreak strain (47). A 5-month outbreak of *C. parapsilosis* fungemia involving 17 neonates in a Taiwanese NICU was caused by two main strains that were genotypically associated with strains isolated from the 20% of staff hand-washing samples that were positive for *C. parapsilosis* (117).

CLINICAL MANIFESTATIONS

Fungemia

C. parapsilosis is among the most common *Candida* species causing invasive disease worldwide (Tables 1 and 2). Table 1 provides an overview of the studies reporting the organisms causing candidemia from 1992 to 2006 as found in PubMed using keywords including *Candida parapsilosis*, candidemia, invasive candidiasis, and fungemia, whereas Table 2 shows specifically the incidence of candidemia in neonates. Figure 1 depicts the total percentages of candidemias due to specific species.

C. parapsilosis fungemia can lead to seeding of tissues, resulting in deep-seated infections (103), and has a mortality rate ranging from 4% (142) to ~45% (34, 52, 108). Data extracted

TABLE 1. Reports of candidemia between 1992 and 2006[a]

Time period	Location	No. (%) of *Candida* isolates						Reference
		Total	*C. parapsilosis*	*C. albicans*	*C. glabrata*	*C. tropicalis*	Other[b]	
1992–1997	United States	1,300	221 (17.0)	660 (50.8)	217 (16.7)	139 (10.7)	63 (4.8)	218
1992–2001	International[d]	6,082	796 (13.1)	3401 (55.9)	984 (16.2)	585 (9.6)	316 (5.2)	211
1993–2002	Japan	158	62 (39.2)	49 (31.0)	19 (12.0)	17 (10.8)	11 (7.0)	186
1994–1995	Taiwan	120	11 (9.2)	60 (50.0)	17 (14.2)	24 (20.0)	8 (6.7)	121
1995–1999	United States	1977	391 (19.8)	733 (37.0)	458 (23.2)	307 (15.5)	88 (4.5)	202
1995–1999	Spain	143	32 (22.4)	63 (44.1)	20 (14.0)	8 (5.6)	20 (14.0)	6
1996–2001	Spain	218	48 (22.0)	91 (41.7)	26 (11.9)	35 (16.1)	18 (8.3)	168
1996–2004	Saudi Arabia	98	16 (16.3)	52 (53.1)	7 (7.1)	19 (19.4)	4 (4.1)	7
1997–1999	Malaysia	102	52 (51.0)	12 (11.8)	4 (3.9)	26 (25.5)	8 (7.8)	189
1997–2001	United States	113	13 (11.5)	68 (60.2)	18 (15.9)	10 (8.8)	4 (3.5)	108
1997–2002	United States	126	19 (15.0)	72 (57.1)	19 (15.0)	15 (11.9)	1 (0.08)	61
1998–2000	United States	1,143	153 (13.4)	516 (45.1)	275 (24.0)	141 (12.3)	58 (5.0)	258
1999–2003	Italy	182	42 (23.1)	74 (40.7)	27 (14.8)	16 (8.8)	23 (12.6)	22
2000–2002	Brazil	50	18 (36.0)	14 (28.0)	2 (4.0)	8 (16.0)	8 (16.0)	174
2000–2004	Italy	294	64 (21.8)	168 (57.1)	26 (8.8)	28 (9.5)	8 (2.7)	273
2001–2005	India	275	55 (20.0)	60 (21.8)	48 (17.5)	97 (35.3)	15 (5.5)	295
2002–2003	Spain	345	78 (22.6)	175 (50.7)	29 (8.4)	34 (9.9)	29 (8.4)	5
2002–2003	Brazil	171	64 (37.4)	107 (62.6)	—[c]	—	—	34
2002–2003	Brazil	282	64 (22.7)	107 (37.9)	9 (3.2)	48 (17.0)	54 (19.1)	51
2003	International[e]	1,397	242 (17.3)	680 (48.7)	240 (17.2)	152 (10.9)	83 (7.1)	177
2003–2004	Brazil	712	146 (20.5)	291 (40.9)	35 (4.9)	149 (20.9)	91 (12.8)	52
2004–2005	Germany	428	40 (9.3)	250 (58.4)	80 (18.7)	27 (6.3)	31 (7.2)	29
2004–2005	Portugal	100	30 (30.0)	41 (41.0)	9 (9.0)	15 (15.0)	5 (5.0)	54
2004–2006	International[f]	397	70 (17.6)	165 (41.6)	119 (30.0)	28 (7.0)	15 (3.8)	114
Total		16,213	2,727 (16.9)	7,909 (48.8)	2,688 (16.6)	1,928 (11.9)	961 (5.9)	

[a] Includes studies with >50 isolates.
[b] Includes *C. lusitaniae*, *C. krusei*, *C. guilliermondii*, *C. dubliniensis*, and *C. rugosa*.
[c] —, no isolates documented.
[d] Includes the United States, Canada, Europe, Latin America, and the Asia-Pacific region.
[e] Includes North America, Europe, and Latin America.
[f] Includes the United States and Canada.

from reports of mortality rates for both *C. parapsilosis* and *C. albicans* reveal that the average mortality rate for *C. parapsilosis* fungemia is 28.5%, while that for *C. albicans* fungemia is 44.8% (Table 3).

From 1983 to 1994, candidemia was detected in 138 patients with hematologic malignancies at an Italian university hospital, and *C. parapsilosis* accounted for 35 (25.3%) of all episodes (103). In a 1995 to 1999 study of nosocomial candidemia episodes in a Spanish tertiary care hospital, *C. parapsilosis* accounted for 32 (22.4%) of 143 cases, while *C. albicans* was attributed to 63 cases (44.1%) (6). A study between 1999 and 2003 performed in an Italian university's ICUs reported 182 incidences of candidemia, where there was an increased incidence of disease over the study period from 1.2 to 3.06/10,000 patient-days/year and 40% of the infections were attributed to *C. albicans* and 23% to *C. parapsilosis* (22). Another Italian study found *C. parapsilosis* in 64 (21.7%) of 294 blood isolates obtained between 2000 and 2004, and the incidence of *C. parapsilosis* isolation increased over the course of the study period (273). In Spain, 218 *Candida* isolates were recovered from blood cultures between 1996 and 2001 (168). Of these, *C. parapsilosis* accounted for 22.0%, outranked only by *C. albicans* (41.7%). Among the 282 episodes of candidemia documented at four tertiary care hospitals in Brazil between 2002 and 2003,

TABLE 2. Reports of neonatal candidemia between 1991 and 2004[a]

Time period	Location	No. (%) of *Candida* isolates						Reference
		Total	*C. parapsilosis*	*C. albicans*	*C. glabrata*	*C. tropicalis*	Other[b]	
1991–2002	Finland	43	28 (65.1)	15 (34.9)	—[c]	—	—	246
1994–1997	Taiwan	46	22 (47.8)	24 (52.2)	—	—	—	118
1994–2000	Greece	58	9 (15.5)	38 (65.5)	1 (1.7)	9 (15.5)	1 (1.7)	232
1995–1998	United States	37	19 (51.3)	15 (40.5)	1 (2.7)	2 (5.4)	—	27
1995–2004	United States	1,997	674 (33.7)	1,157 (57.9)	40 (2.0)	76 (3.8)	50 (2.5)	90
1996–2000	Israel	60	16 (26.7)	40 (66.7)	3 (5.0)	1 (1.7)	—	158
Total		2,241	768 (34.3)	1,289 (57.5)	45 (2.0)	88 (3.9)	51 (2.3)	

[a] Includes studies with >30 isolates.
[b] Includes *C. lusitaniae*, *C. krusei*, *C. guilliermondii*, *C. dubliniensis*, and *C. rugosa*.
[c] —, no isolates documented.

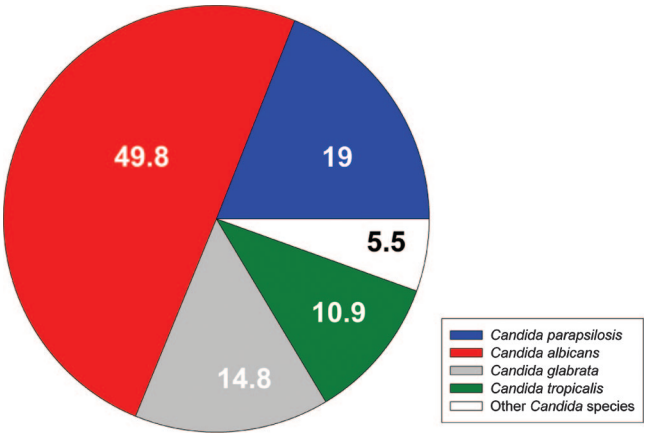

FIG. 1. Percentages of candidal bloodstream isolates from 1991 to the present, calculated from Tables 1 and 2 (total = 18,454). The group "other candidal species" includes *C. lusitaniae*, *C. krusei*, *C. guilliermondii*, *C. dubliniensis*, and *C. rugosa*.

64 (23%) were caused by *C. parapsilosis* and 107 (38%) were due to *C. albicans* (34). From eight Korean university hospitals over a 6-month period, 143 *Candida* bloodstream isolates were recovered, with *C. albicans* (49%) and *C. parapsilosis* (22%) being the most frequently isolated species (152).

A 2002 to 2003 analysis of fungemia in Barcelona, Spain, found that that *C. parapsilosis* accounted for 23% of all cases, and 51% were associated with intravenous catheters (5). Clinically, *C. parapsilosis* infections were characterized by fever (100%), septic shock (22%), and renal failure (10%). The underlying diseases were malignancy (27%), transplantation (16%), and diabetes mellitus (9%). Compared to *C. albicans*, *C. parapsilosis* more frequently caused fungemia among neonates (20% versus 4%) in patients with intravenous lines or vascular catheters who had received prior antifungal agents (26% versus 7%), were on parenteral nutrition (54% versus 33%), or had undergone transplantation (16% versus 2%). *C. albicans* occurred more often in elderly patients (54% versus 27%) and diabetic patients (25% versus 9%).

In some cases, *C. parapsilosis* has outranked *C. albicans* as the dominate species causing candidemia. For instance, over the course of a 7-year study conducted in New Hyde Park, NY, 81 episodes of candidemia were identified in 80 children, and *C. parapsilosis* was isolated in 49% (156). From 1997 to 1999 in the University Hospital of Malaysia, *Candida* species were responsible for 102 positive blood cultures, of which 51% were identified as *C. parapsilosis* and only 11.8% as *C. albicans* (189). A wide range of 1,006 clinical yeast blood isolates investigated between 1999 and 2001 in South America showed that *C. parapsilosis* represented 34.9% of all isolates, while *C. albicans* accounted for 30.2% (183). In a study from January to February 2006 in Fortaleza, Ceara, Brazil, that analyzed 50 blood cultures from 40 candidemic patients, *C. parapsilosis* was identified in 18 cultures whereas only 14 grew *C. albicans* (174).

Among reports specifically describing incidences of neonatal candidemias, *C. parapsilosis* is commonly identified as a major cause of disease (Table 2). The largest study included 128 NICUs and 130,523 patients, in which 1,997 *Candida* bloodstream infections were identified between 1995 and 2004, mostly in infants under 1,000 g. *C. parapsilosis* accounted for 33.7% of candidemia infections, representing the second most common species after *C. albicans* (57.9%) (90). Furthermore, a 1998 report documented an 11-fold increase in candidemia caused by *C. parapsilosis* in an NICU between 1981 and 1995 (142).

Outbreak cases of *C. parapsilosis* fungemia often originate from contaminated sources used by multiple patients. Early reports attributed *C. parapsilosis* infections to contaminated albumin and hyperalimentation solutions as well as to intravascular pressure-monitoring devices (221, 260, 261, 287, 290). More recent studies have provided further insight on *C. parapsilosis* fungemia outbreaks. A cluster of *C. parapsilosis* fungemia infections in a NICU in Louisiana was attributed to the administration of contaminated liquid glycerin, although cultures of the original bottles were not obtained (290). Importantly, as mentioned in Risk Factors above, cross-infection during contact between patients and health care providers has been a significant cause of nosocomial outbreak infections. Between 1988 and 2000 in a tertiary care hospital in Spain, *C. parapsilosis* was the most isolated *Candida* species in the pediatric intensive care unit, due to the four *C. parapsilosis* outbreaks that occurred during the study period (245). Overall, *C. parapsilosis* accounted for 109 (32.9%) of all candidemia cases in the hospital and pediatric ICU, compared to 169 (51.1%) episodes caused by *C. albicans*, yet the proportion of *C. parapsilosis* infection in both the hospital and the pediatric ICU increased over the course of the study, while the incidence of *C. albicans* remained stable.

TABLE 3. Mortality rates associated with *C. parapsilosis* and *C. albicans* fungemia

Species	% Mortality (total no. of cases)	Reference
C. parapsilosis	4 (54)	142
	16 (32)	6
	46 (13)	108
	11 (9)	232
	23 (78)	5
	45 (64)	34
	45 (146)	52
	14 (153)	258
	25 (16)	7
	39 (23)	49
	38 (64)	273
	30 (30)	54
Avg	28.5	
C. albicans	26 (50)	142
	39 (63)	6
	62 (68)	108
	40 (38)	232
	43 (175)	5
	62 (107)	34
	57 (291)	52
	31 (516)	258
	50 (52)	7
	42 (50)	49
	58 (168)	273
	46 (41)	54
Avg	44.8	

Endocarditis

Fungal endocarditis accounts for 1.3% to 6% of all infective endocarditis cases, and its incidence has increased over the past 2 decades as a result of improvements in diagnosis due to better culture systems, the use of transesophageal ultrasound, and the increase in intensity of medical therapies that predispose patients to fungal infection (99, 220). *Candida* species account for 94.1% of fungal endocarditis cases, many of which develop following cardiac surgery (203), and *C. parapsilosis* is associated with 17% of the identified cases, making it the second most common species after *C. albicans* (99). Of 56 *C. parapsilosis* endocarditis cases reviewed in 1992, 50% of patients had a history of intravenous drug use related to their infection and 60% had a preexisting valvular disease (286).

Currently, the most common predisposing factors for *C. parapsilosis* endocarditis include prosthetic valves (41/72, 57.4%), intravenous drug use (12/72, 20%), intravenous parenteral nutrition (6.9%), abdominal surgery (6.9%), immunosuppression (6.4%), treatment with broad-spectrum antibiotics (5.6%), and previous valvular disease (4.8%) (99). Individual case reports have included intravenous catheters (127, 241), hyperalimentation solution (127, 241), antibiotic therapy (40, 127, 241), bone marrow transplant (38), and abdominal surgery (127) as risk factors. Endocarditis due to *C. parapsilosis* most often arises in the setting of fungemia, as damaged tissues are more prone to infection (38). The cardiac tissue most commonly infected is the aortic valve (56.9%), followed by the mitral valve (29.1%), tricuspid valve (4.1%), ventricular wall (2.8%), and pulmonary valve (1.4%) (99).

C. parapsilosis endocarditis has a mortality rate and frequency of dissemination similar to those for *C. albicans* fungemia (286). Overall, mortality ranges from 41.7% (94) to 65% (286). Unfortunately, the ideal treatment for *Candida* endocarditis remains undetermined. The current documented mortality rate for patients treated medically by antifungal agents alone is 53.3% (99), which is decreased from 78% in 1992 (286). Combined surgical debridement and replacement of the infected valve, whether native or prosthetic, in conjunction with aggressive antifungal therapy has been associated with the lowest mortality rates (103, 127, 286). However, there are differences of opinion in regard to treatment options, especially when individual case reports detail successful treatment of endocarditis with antifungal agents alone and argue that surgery is not necessarily needed in all endocarditis infections involving prosthetic heart devices. For instance, a recurrent case of endocarditis involving a prosthetic mitral valve was unsuccessfully treated with amphotericin B but cleared by amphotericin B colloidal dispersion followed by fluconazole for 8 months (154). Antifungal therapy alone also proved successful in other instances where either surgery was not chosen for treatment or the patient was not a candidate for surgical intervention (13, 127, 241, 300). However, case reports are biased to disclosing positive rather than negative clinical outcomes. Hence, given the tenacity of *C. parapsilosis* biofilms, particularly when prosthetics are involved, and that the best outcomes for endocarditis were achieved in patients treated surgically with concomitant aggressive antifungal medications, it is reasonable, if medically feasible, to recommend that patients receive combination therapy with surgery and antifungals for *C. parapsilosis* endocarditis.

Meningitis

Fungal infections of the central nervous system pose serious, life-threatening risks and can be caused by a number of fungi. Classic symptoms include headache, photophobia, nuchal rigidity, fever, and delirium. *Candida* species typically cause acute neutrophilic meningitis, whereas chronic lymphocytic meningitis and granulomatous meningitis are more commonly associated with *Cryptococcus neoformans* and *Coccidioides* species, respectively (41). Autopsy studies of adults with invasive candidiasis have revealed that fewer than 15% develop meningeal disease (159). On the other hand, it has been reported that 64% of neonates who die from invasive candidiasis have central nervous system involvement (78).

C. parapsilosis is an infrequent cause of fungal meningitis. Among various reports reviewing candidal meningitis cases from 1966 to 1994, 116 infections (90.1%) were due to *C. albicans*, while *C. parapsilosis* meningitis only occurred twice (1.6%) (24, 45, 70, 78, 159, 280). Further, a review of candidal meningitis among neonates at the Texas Children's Hospital in the period from 1989 to 1999 shows that of 106 neonates with systemic candidiasis, only 23 (21.7%) developed candidal meningitis, none of whom were infected with *C. parapsilosis* (85). However, between 1998 and 2001, *C. parapsilosis* was the causative agent of 3 (23.1%) of 13 cases of nosocomial candidal meningitis in Slovakia, while *C. albicans* was isolated seven times (53.8%) (74). Among the patients infected with *C. parapsilosis*, two were premature children and the other was a child with epilepsy. Individual cases of *C. parapsilosis* meningitis have also been documented (30, 77, 124). Nevertheless, given the increasing incidence of *C. parapsilosis*, it is necessary to maintain vigilance for the development of meningitis in neonates due to the potential morbidity and mortality associated with disease.

Peritonitis

Fungal peritonitis causes serious morbidity and has a mortality rate of up to 44% (285). It occurs in 3% to 10% of patients with end-stage renal disease treated with continuous ambulatory peritoneal dialysis (CAPD) (167, 285). The major predisposing factor for fungal peritonitis is treatment of previous bacterial peritonitis by antibiotics, which presumably promotes fungal overgrowth (9). Additional studies show that 87.3% of 55 patients with fungal peritonitis (105) and 71.4% of 7 patients with infection specifically due to *C. parapsilosis* (293) had previously received antibiotics. Of 23 patients receiving CAPD in Thailand, 18 developed *C. parapsilosis* peritonitis after a median time of 1.03 months following bacterial peritonitis, 12 of whom were still receiving systemic antibiotics at the time of diagnosis (126). Clinically, *C. parapsilosis* peritonitis is associated with cloudy diasylate effluent, abdominal pain, fever, and bowel obstruction, symptoms similar to those of other peritonitis infections caused by *Candida* species as well as bacteria (126, 285, 293). Thus, the causative agent of fungal peritonitis may be incorrectly diagnosed as a bacterial patho-

gen, resulting in the administration of systemic antibacterial agents and further progression of fungal disease.

Although *C. albicans* is credited as the most common *Candida* species causing peritonitis, numerous papers have reported that *C. parapsilosis* is the predominant species associated with disease in patients receiving CAPD. A 3-year study in Jerusalem, Israel, found that *C. parapsilosis* was responsible for 43.8% of all fungal peritonitis infections (299). The same study cites a higher prevalence of *C. parapsilosis* infection among pediatric patients on CAPD (22 of 33 [66.6%]) than among adults on CAPD (3 of 24 [12.5%]). In a 1989 to 1998 study of 896 patients receiving CAPD, 70% of the 70 episodes of fungal peritonitis were caused by *Candida* species and half of these 70% were caused by *C. parapsilosis* (285). Of 10 cases of fungal peritonitis caused by yeasts in Mexico City between 1997 and 2001, *C. parapsilosis* was found three times, equal to the number of infections caused by *C. albicans* (167). A 2004 Taiwanese report listed *C. parapsilosis* as the most common pathogen causing fungal peritonitis (29%), while *C. albicans* accounted for 14% (43). In 2006, *C. parapsilosis* accounted for 9 episodes of peritonitis (41%) in 22 patients with fungal peritonitis among 762 peritoneal dialysis patients in Taiwan (44). In 1992, an outbreak of fungal peritonitis in 12 CAPD patients in Birmingham, United Kingdom, was attributed to *C. parapsilosis* colonization of the CAPD unit and medical ward and was believed to have originated in pigeon excreta from the windowsills (107).

Treatment for *C. parapsilosis* peritonitis remains controversial and is understudied. Catheter removal is thought to be important considering the propensity of the pathogen to form biofilm as well as the promotion of growth and biofilm formation in high-glucose environments such as the peritoneal cavity (126). Furthermore, *C. parapsilosis* is associated with a higher complication rate than other *Candida* species (78% versus 20%), involving abscess formation and prolonged peritonitis despite catheter removal (44). The same report showed that among patients receiving fluconazole as monotherapy, the rate of complication for *C. parapsilosis* peritonitis was substantially higher (100%) than that for peritonitis caused by other *Candida* species (29%). Thus, intensive systemic antifungal therapy is needed in the case of *C. parapsilosis* peritonitis.

Arthritis

Fungal arthritis occurs infrequently and is most often associated with *Candida* species. The majority of cases involve direct intra-articular inoculation of *Candida* species to a joint, particularly in elderly patients (56, 153). Although rarer, arthritis complicating disseminated candidiasis can occur, especially in immunosuppressed individuals, and has a worse prognosis than disease due to direct inoculation (60, 80, 116, 153).

Individual case reports show that *C. parapsilosis* most often infects joints following implantation of prostheses or after arthrocentesis. By 1992, only eight cases of infectious arthritis due to *C. parapsilosis* had been identified, seven of which followed instrumentation of joints for placement of a joint prosthesis, joint injection, or arthrocentesis (286). Case reports on *C. parapsilosis* arthritis illustrate the difficulty in treating this disease, as evidenced by the large number of recurrent episodes of infection. In 1993, a patient with human immunodeficiency virus (HIV) developed *C. parapsilosis* prosthetic arthritis in his knee, which could not be cured by resection arthroplasty, intravenous amphotericin B, and suppressive ketoconazole therapy (274). Subsequent protracted treatment with fluconazole proved effective, although subsequent joint instability required above-the-knee amputation. Fluconazole alone, administered first intravenously and then orally for 4 weeks and then maintained at a lower dosage for life, proved an effective treatment for a 73-year-old woman who developed *C. parapsilosis* arthritis 30 months after total joint arthroplasty of the right knee (57). In another case, a 77-year-old man was diagnosed with a *C. parapsilosis* infection 4 weeks following total knee arthroplasty. The early identification of infection prevented removal of the firmly attached prosthesis, and the patient was treated by debridement and lavage of the joint, continuous irrigation with fluconazole for a period of 4 weeks, and oral fluconazole for the following 6 months (282). Another successful salvage of a primary arthroplasty following a *C. parapsilosis* joint infection occurred in 1998 when a 64-year-old man underwent total knee arthroplasty (36). Nevertheless, removal of prosthetic joints infected with *C. parapsilosis*, particularly if the diagnosis of candidal arthritis occurs in the chronic stage, is often necessary. In a *C. parapsilosis* infection of a prosthetic knee joint, successful treatment involved removal of the prosthesis, thorough debridement, and fluconazole therapy for 10 weeks (298).

Although the majority of fungal arthritis cases involve prosthetic devices or invasive procedures on later-infected joints, infections have occurred in otherwise healthy joints. An interesting instance of *C. parapsilosis* arthritis occurred in a 38-year-old female kidney transplant recipient without a history of instrumentation who developed swelling, tenderness, and decreased range of motion of the knee and received antibiotics for presumptive bacterial arthritis. Upon isolation of *C. parapsilosis* from joint fluid, arthroscopic irrigation and debridement were performed, followed by systemic and local administration of amphotericin B, oral flucytosine, and fluconazole; however, the intravenous amphotericin B was replaced by weekly intra-articular injections of amphotericin B. This therapy was later replaced by lifelong maintenance with fluconazole and flucytosine (278). A patient with HIV treated with fluconazole for a *C. albicans* fungemia infection was later diagnosed with *C. parapsilosis* arthritis of the shoulder joint (153). The *C. parapsilosis* was resistant to fluconazole therapy but was eradicated with caspofungin.

Ocular Infections

C. parapsilosis is associated with invasive ocular diseases such as endophthalmitis (particularly postoperative infection) and keratitis. *C. parapsilosis* endophthalmitis has followed cataract extraction and corticosteroid eye drop use (234), extracapsular cataract extraction, intraocular lens implantation and administration of topical and subtenonian steroids (102), and intracapsular cataract extraction (266). Further, a 1983 outbreak of *C. parapsilosis* endophthalmitis affecting 30 cataract extraction patients across four states in the United States was caused by contaminated balanced salt eye irrigation solutions (172, 197, 265).

Endogenous fungal endophthalmitis is currently relatively

uncommon, even in the setting of systemic disease. For instance, in a prospective study between 1995 and 2000, an incidence of endogenous fungal endophthalmitis of only 2% was reported from a city hospital in St. Louis, MO (83). *C. parapsilosis* was the fifth most common fungal species causing eye infections. The currently low endophthalmitis frequency is attributed to earlier microbiological identification and diagnosis of systemic candidal disease along with more aggressive and potentially less toxic treatment regimens against fungal sepsis.

Due to the paucity of patients with *C. parapsilosis*, endophthalmitis therapy has not been standardized. Of 11 patients with eye infections found in corneal smears, conjunctival swabs, and vitreous fluid, *C. parapsilosis* caused endophthalmitis only once, while five strains of *C. albicans* were isolated (73). In 2003, a 39-year-old woman who underwent keratoprosthesis surgery developed *C. parapsilosis* endophthalmitis 2 years postoperatively, which was successfully treated with oral fluconazole and topical amphotericin (19). An interesting case of recurrent endophthalmitis arose after phacoemulsification and posterior chamber intraocular lens implantation, during which the patient developed secondary keratitis despite aggressive medical and surgical treatments for *C. parapsilosis* infection (81). Recurrent episodes occurred, with the development of an intracapsular plaque and infectious nidus on the corneal endothelium; treatment was by debridement and intraocular and topical amphotericin B. Interestingly, four patients with *C. parapsilosis* endophthalmitis following intraocular lens implantation were treated with fluconazole; however, only the patient who had the lens implant removed was cured of infection after 1 year of treatment (132). Another patient with *C. parapsilosis* endophthalmitis underwent bilateral pars plana vitrectomy, total capsulectomy, intraocular lens exchange, intravitreal injection of amphotericin B, and oral fluconazole therapy in 1997 (294). *C. parapsilosis* has also caused crystalline keratopathy in a corneal graft (229), supportive stromal keratitis (31, 233, 272), and keratitis after laser in situ keratomileusis (LASIK) (259).

The clinical manifestations seen in keratitis vary greatly from patient to patient; however, the clinical presentations of *C. parapsilosis* keratitis include redness, photophobia, pain, decreased vision, and a yellow-white infiltrate with dry raised slough and feathery edges, and severe disease results in wet, necrotic stromal inflammation with features indistinguishable from those of other forms of microbial keratitis (31).

Otomycosis

Otomycosis is a relatively uncommon infection causing otitis media or externa (inflammation of the middle ear or outer ear, respectively); persistent white or colorless otorrhea with tympanum perforation; edema and erythema of tympanic membrane residuum; ear pain; increasing hearing loss; and whitish, cotton-like or greasy debris in the external auditory canal, tympanic membrane, or (following excision of cholesteatoma) residual space (279). Recent evidence shows that the middle ear of immunocompetent patients suffering from chronic hyperplastic (polypoid) inflammation is especially susceptible to infection with pathogenic fungi, as the increased production and buildup of mucus promotes colonization (279).

During a 1-year study in Spain, *C. parapsilosis* was associated with disease in 42.9% of 40 identified otomycosis patients, in whom risk factors included sea bathing (90%), trauma (27.5%), and prior antimicrobial treatment (40%) (98). From 1993 to 2000, 128 otomycosis patients were identified, and *C. parapsilosis* accounted for more than half of all yeasts causing disease, which was double the number of *C. albicans* infections (279). In contrast, of 40 Slovakian patients with otomycosis, 11 (27.5%) were infected with *C. parapsilosis*, while *C. albicans* was identified in 21 (52.5%) (72). Between 1996 and 2003, 166 of 1,242 children evaluated at a university hospital in Wisconsin for otitis had positive ear cultures for fungal organisms; 23.5% were *C. parapsilosis*, while *C. albicans* accounted for 43.4% (170). Development of fungal otitis in children was significantly associated with prior oral and ototopical antibacterial agents, with the greatest increase seen after the widespread use of ofloxacin in the clinic.

The relevance of fungal isolation from the ear in relationship to disease as opposed to commensalism has been questioned (79). However, a correlation between fungal infection and chronic inflammation of the ear has been made, as inflammation, such as erythema, edema, and desquamation of meatal epithelial tissues, resolved in all patients treated with topical antimycotic regimens (279). Aggressive use of antibacterial agents, such as topical quinolone antibiotics, within the ear may be a factor in the occurrence of fungal ear infections (170, 250). Successful treatment for mycosis of the auditory canal has included intense debridement and cleansing in combination with topical clotrimazole for a period of 7 to 14 days, although tympanic membrane infections require up to 4 weeks of treatment (279).

Onychomycosis

Onychomycosis is a nail infection caused by dermatophytes, yeasts, and molds. According to some investigators, onychomycoses can comprise 30% of all superficial fungal infections and up to half of all nail disorders (251). Onychomycosis predominantly affects adults, especially persons >50 years of age, as an increase in nail plate thickness and a decrease in nail growth rate make these individuals more susceptible to infection, although infections have also occurred in neonates (141). Risk factors for *C. parapsilosis* nail infection include previous traumatic dystrophy of the nail and exposure to soil during activities such as gardening (100). General clinical manifestations of *Candida* nail infections include total dystrophic onychomycosis (seen mostly in chronic mucocutaneous candidiasis), proximal and lateral nail dystrophy (secondary to chronic paronychia), and distal and lateral nail dystrophy (associated with onycholysis and peripheral vascular disease) (111, 251). Further clinical manifestations are hyperkeratosis of the nail plate with distortion of the normal curvature and distal erosion, chronic proximal paronychia with irregular transverse grooves and ridges and discoloration of the lateral margin, and isolated distal and lateral onycholysis (48, 100). Clinical observations specific to reports of *C. parapsilosis* nail infections are associated with distal nail disease, in contrast to the case for *C. albicans* which is more prominent in proximal subungal onychomycosis or total dystrophic onychomycosis (182, 251, 301). A rare case of *C. parapsilosis* onychomycosis in which melanonychia was present has also been described (100).

Previously, *C. parapsilosis* was seldom mentioned as an agent

causing pathological lesions of the nails, but it has gained increasing recognition as the most common etiological agent causing *Candida* onychomycosis. For instance, in a 1988 analysis of the composition of microflora in the subungal space of the hand, 69% of 26 adult volunteers tested positive for yeast and *C. parapsilosis* comprised 51.3% of the isolates (173). Since *C. parapsilosis* is one of the main species of microflora inhabiting the subungal space, it can be argued that its isolation is a result of transient colonization on the surfaces of nails, including nails infected by other *Candida* species. Despite its role as a commensal, however, multiple reports continue to document the increase in *C. parapsilosis* onychomycosis. In a study of 1,006 clinical isolates from a wide range of clinical samples in Argentina and Paraguay, *C. parapsilosis* was the most common candidal species (37.7%, versus 22.0% for *C. albicans*) causing onychomycosis (183). Of 200 candidal isolates from patients with fingernail infections between 2004 and 2005 in Brazil, *C. parapsilosis* was found in 81 samples (40.5%) (86). Between 1990 and 2001 in a study involving 5,077 nail samples from 4,177 patients in Germany, fungi were detected on 54% of the examined nail samples, and the causative agents of onychomycosis included dermatophytes (68%), yeasts (29%), and molds (3%) (182). Notably, yeasts accounted for 56% of fingernail onychomycoses, nearly all of which are caused by *Candida* species (96.1%). *C. parapsilosis* was the leading yeast pathogen infecting fingernails (50%) and toenails (39%) and the second most common overall causative agent of onychomycosis (12%), following the dermatophyte *Trichophyton rubrum*.

Vulvovaginitis

C. parapsilosis remains an infrequent cause of fungal vulvovaginitis (286). Vaginal candidosis is the second most common vaginal infection in the United States, after bacterial vaginosis (256), and *C. albicans* is associated with 85% to 95% of cases. Recently there has been an increase in non-*C. albicans* vulvovaginal cases, which is linked to the widespread use of short-course topical and oral azole anitmycotics as well as the abuse of over-the-counter antifungal medications available in the United States (195, 230, 256, 257). Furthermore, as many as 30% of recurrent vulvovaginal candidoses are caused by non-*C. albicans* species (196). Therefore, proper identification of the *Candida* species should be undertaken in patients with recurrent or complex vulvovaginitis before initiation of short-course antifungal treatment, which may be less effective against recurrent non-*C. albicans* species (23, 195, 230). It is noteworthy that although *C. parapsilosis* is infrequently isolated by vaginal culture, it nevertheless may be isolated from asymptomatic women (195, 230).

In a study involving 163 female sex workers with histories of candidal vaginosis over a 4-year period in Spain, *Candida* species were isolated in 1,967 samples (18.5% of the total), of which *C. albicans* accounted for 89.3% of isolates while *C. parapsilosis* was rarely identified (1.2%) (204). Lower incidences of *C. albicans* were found among pregnant Tanzanian women with vaginal candidiasis (66.2%), although *C. parapsilosis* was still isolated rarely (2.2%) (187). Of 123 positive vaginal swabs taken from 612 patients, of whom only 39 had clinical vaginal candidiasis, from the outpatient obstetrics and gynecology clinic of a university hospital in Belgium, *C. albicans* was the most commonly isolated species (68.3%), while *C. parapsilosis* was the third most frequent species (8.9%) (23). Similar rates were seen in vaginal cultures taken from 140 women in Jordan (2). Between 2001 and 2002, 635 isolates were identified from 582 vaginal cultures obtained at the Drexel University College of Medicine in the United States, 54 (8.5%) of which were *C. parapsilosis* (195). Similarly, 5.1% of 593 vaginal yeast isolates were *C. parapsilosis* and 70.8% were *C. albicans* in a study performed at the University of Iowa (230).

The role of *C. parapsilosis* as a vaginal pathogen and its relevance to symptoms of vulvovaginitis are questionable, particularly because of its documented role as a commensal yeast (195, 230). Interestingly, *C. parapsilosis* and *C. albicans* isolates associated with vulvovaginitis secrete more aspartyl proteinases in vitro than organisms isolated from asymptomatic carriers (4). This is significant because acid proteinases can compromise the normal integrity of the vagina by hydrolyzing mucosal immunoglobulin A, one of the vagina's most effective barriers against infection, and are thus potential powerful microbial virulence factors contributing to the pathogenic capacity of both *C. albicans* and *C. parapsilosis* (64). Furthermore, *C. parapsilosis* virulence has been demonstrated in a rat vaginal infection model, where a clinical vaginitis *C. parapsilosis* strain exhibited pathogenesis similar to that of a *C. albicans* isolate (63). Additional evidence of the pathogenic role of *C. parapsilosis* in the vagina comes from a study showing that 65% of 54 infected women experienced symptomatic relief after clearance of the yeast using fluconazole, buconazole, miconazole, or boric acid (195). Patient symptoms included itching (53%), burning (43.1%), dyspareunia (31.4%), and abnormal discharge (21.6%), while 20% of patients were asymptomatically colonized with *C. parapsilosis*.

Urinary Tract Infections

The reported incidence of urinary tract infections caused by *Candida* species varies. For instance, among 6,281 strains of urinary tract pathogens isolated from hospital inpatients in Brescia, Italy, between 2002 and 2005, only 56 (0.9%) were *Candida* species (66). Interestingly however, over the course of the study, the isolation rate significantly increased, ranging from 0.5% to 1.4%. Other reports have claimed that *Candida* species cause between 10% and 15% of hospital urinary tract infection (8, 59, 288) and that 22% of patients requiring a stay of 7 days or more in the ICU developed candiduria (8). Some authors have also noted an increase in the prevalence of candiduria, given that by the end of the 1980s *Candida* species accounted for 7% of all nosocomial urinary tract infections, while a 1-year study published in 2004 and including 205 inpatients found an incidence of 22% (59, 138, 281). It is significant to note that the presence of *Candida* in urine does not necessarily reflect disseminated disease but could result from colonization of the lower urinary tract. Thus, *Candida* species have been isolated from asymptomatic patients, for whom the necessity of antifungal therapy is questionable (59, 104).

Among *Candida* species, *C. parapsilosis* is not a frequent cause of urinary tract infection. Among the 45 nosocomial infections identified in the study mentioned above, *C. parapsilosis* was the causative agent in four cases, behind *C. albicans*

($n = 16$), *C. tropicalis* ($n = 10$), and *C. pseudotropicalis* ($n = 5$). The rate of *C. parapsilosis* urinary tract infections was similar in a study of 100 candiduria cases in a pediatric hospital in Sao Paulo, Brazil, from 1999 to 2004 (59). In this case, *C. parapsilosis* was isolated four times, being outranked by *C. albicans* ($n = 56$), *C. tropicalis* ($n = 20$), and *C. glabrata* ($n = 11$) (59). An interesting 1994 case report documented a neonate suffering from renal fungus balls caused by *C. parapsilosis* which could not be eradicated by amphotericin B but was later cured with fluconazole (289).

VIRULENCE FACTORS

The pathogenesis of invasive candidiasis is facilitated by a number of virulence factors, most importantly adherence to host cells, biofilm formation, and secretion of hydrolytic enzymes, such as proteases, phospholipases, and lipases. Despite intensive research to identify pathogenic factors in fungi, particularly in *C. albicans*, relatively little is known about the virulence determinants of *C. parapsilosis*. This is a major deterrent to the diagnosis, treatment, and prevention of diseases caused by *C. parapsilosis*.

Adherence

Colonization and infection with *C. parapsilosis* are dependent upon the ability of the fungus to adhere to host cells and tissues, particularly mucosal surfaces. Adherence to indwelling medical devices facilitates the formation of biofilm and promotes host damage. Cell surface hydrophobicity has been associated with the initial adherence of *C. parapsilosis* to surfaces (206), and the production of slime has been linked to the tendency of *C. parapsilosis* to adhere to plastic catheters (32).

The first large-scale study comparing *C. albicans* and *C. parapsilosis* (12 and 24 isolates, respectively) adhesion documented a 20.6% greater avidity of *C. parapsilosis* for buccal epithelial cells (BEC) and a 143.7% greater adhesion to acrylic material, although the differences between the BEC values were not significant due to the large range of *C. parapsilosis* adhesion values (23.50 to 154.30 per 50 BEC) (206). In contrast, other, smaller studies attributed an 80% to 95% higher tendency for *C. albicans* adhesion to BEC versus *C. parapsilosis* (20, 137); these studies each used only a single *C. parapsilosis* isolate, making the relevance of their findings questionable. However, the large number of adherent *C. parapsilosis* cells reported previously (206) may be a result of coadherence among yeast cells causing aggregates on epithelial surfaces, a trait more often observed for this fungus than for *C. albicans*. Furthermore, there is significant intraspecies variation in adherence. Although the result was not statistically significant, superficial *C. parapsilosis* isolates had 51.5% greater avidity for BEC than systemic isolates (206). Additionally, *C. parapsilosis* strains with similar pathogenicities in an experimental vaginal infection varied in their capacities to adhere to plastic (39). Hence, adhesion to plastic is not an unequivocal virulence factor related to vaginopathic potential or systemic infection, although adherence in vivo may be relevant for infection (62).

Biofilm Formation

Biofilms are surface-associated communities of microorganisms within an extracellular matrix and are the most prevalent type of microbial growth (146). The generation of *C. albicans* biofilm is associated with the dimorphic switch from yeast to hyphal growth, and the structure of the formed biofilm involves two distinct layers: a thin, basal yeast layer and a thicker, less compact hyphal layer (14). In contrast, *C. parapsilosis* strains produce quantitatively less and structurally less complex biofilm than *C. albicans* (110, 145). Certain filamentous (pseudohyphal) *C. parapsilosis* phenotypes, however, generate more biofilm and are more invasive into agar than strains remaining predominantly in the yeast form (150).

Formation of biofilm is preceded by adherence to tissues or medical devices, presumably resulting in a change in organism morphology and behavior. *C. parapsilosis* biofilms can occur on diverse medical devices, including central and peripheral venous catheters, hemodialysis and peritoneal dialysis catheters, intracardiac prosthetic devices, and prosthetic joints (224). As a commensal of human skin, the organism can come into contact with medical devices prior to or during patient use, particularly in health care environments where lapses in proper hand hygiene occur. It is noteworthy that *C. parapsilosis* isolates with increased biofilm have been associated with outbreaks (147).

Biofilm formation is a potent virulence factor for a number of *Candida* species, as it confers significant resistance to antifungal therapy by limiting the penetration of substances through the matrix and protecting cells from host immune responses. Biofilm-forming *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. glabrata* isolates have been associated with significantly higher mortality rates in patients at an Italian university hospital compared to patient isolates incapable of forming biofilm (70.0% versus 45.7%, respectively) (273). Specifically for *C. parapsilosis*, the mortality rate for isolates forming biofilm in vitro was 71.4%, as opposed to 28% for biofilm-deficient isolates.

The capacities of different *C. parapsilosis* isolates to cause disease in various tissues may be influenced by their ability to form biofilm. In one study, 86% of *C. parapsilosis* blood isolates were capable of forming biofilm, compared to 47% of isolates from other body sites (254). A second study found that 59% of bloodstream isolates produced biofilm, versus 39% of skin isolates (238). In contrast, another study found that only 21.8% of blood isolates were capable of forming biofilm (273). The variation in results may be due to conditions used to assess biofilm production and to the length and method of strain storage prior to study.

Two recent studies documenting the generation of *C. parapsilosis* homozygous knockout mutants found that the mutants have a decreased ability to form biofilm. *C. parapsilosis* lipase knockout mutants produced significantly less biofilm than a wild-type strain (97), and the *BCR1* gene was necessary for proper biofilm formation (71). Notably, the biofilm-deficient *C. parapsilosis* lipase mutants were less virulent in tissue culture and during murine infection (97).

There are extensive data demonstrating the resistance of *Candida* species in biofilm to antimycotic drugs (67). Despite its less complex structure, *C. parapsilosis* biofilm is similarly

resistant as *C. albicans* biofilm to conventional antifungals, such as amphotericin B and azole compounds, (131, 238). However, therapeutic levels of echinocandins can inhibit metabolic activities of *C. parapsilosis* biofilms (50, 131, 146), and lipid formulations of amphotericin B have shown activity against *C. parapsilosis* biofilm (146).

Farnesol is a quorum-sensing agent in *C. albicans* that inhibits biofilm formation as well as filamentation (115, 225). Farnesol has similar effects on *C. parapsilosis*, in that biofilm formation is inhibited if farnesol is added to polystyrene wells prior to inoculation with the fungus, but the compound does not prevent formation if added after adherence of the fungi occurs (150). Hence, quorum sensing is involved in *C. parapsilosis* biofilm formation and is an area ripe for further study.

Medical devices infected with *C. parapsilosis* usually require removal for fungal clearance, although some single-case studies report successful treatment of biofilm-associated infections with antifungal therapy alone (146, 176, 190, 228). Additional research on agents with activity against biofilms is necessary, as such drugs could greatly aid in catheter-related infections while potentially reducing the number of surgical procedures necessary in clinical cases such as endocarditis and arthritis.

Secreted Enzymes

In recent years extracellular secreted enzymes of microbial pathogens have gained significant attention for their potential role in pathogenesis and as possible targets for the design of synthetic inhibitors to treat infection. These include aspartic proteinases, (Saps), phospholipases, and lipases.

Secreted aspartic proteinases. The secretion of aspartic proteinases (Sap1p to Sap10p) is an important virulence determinant of *C. albicans* (119, 149, 179, 185, 263, 269). Saps facilitate invasion and colonization of host tissue by disrupting host mucosal membranes (237) and degrading important immunological and structural defense proteins, such as immunoglobulin G heavy chains, α_2-macroglobulin, C3 protein, β-lactoglobulin, lactoperoxidase, collagen, and fibronectin (219). Compared to *C. albicans*, *C. parapsilosis* has less Sap activity (198, 236). Three Saps have been identified in *C. parapsilosis*, two of which remain largely uncharacterized (175). The Sapp1p isoenzyme has been biochemically characterized (75, 92, 219). Although originally classified as a pseudogene, *SAPP2P* produces a functional proteinase, Sapp2p, which constitutes about 20% of the Saps isolated from a culture supernatant (93). Further, the proteolytic activity of the *SAPP2P* gene product has a different activation mechanism than that of the *SAPP1P* product (175). No studies have analyzed or characterized *SAPP3* or Sapp3p.

Sap production varies among isolated strains of *C. parapsilosis*, and Sap involvement in pathogenesis remains unclear. However, there is a trend relating Sap production and site of isolation in that both vulvovaginal and skin isolates of *C. parapsilosis* exhibit higher in vitro Sap activity than blood isolates (39, 58, 62, 65, 297). This has significant implications for infection models. For example, in vaginal rat infections, blood *C. parapsilosis* isolates are cleared during the first or second week postchallenge, while skin isolates produce sustained infection (62). Further, no significant differences in vaginopathic potential are found between vaginal *C. parapsilosis* isolates with high Sap production and a vaginopathic *C. albicans* isolate (63). Hence, Saps appear to be less important for pathogenesis in bloodstream infection than in localized invasive disease, particularly in vaginal infections. Interestingly, *C. parapsilosis* strains ($n = 4$) isolated from patients with candiduria in Sao Paulo, Brazil, all exhibited proteolytic activity (59).

Inhibitors of Saps have been tested as antimycotic drugs. Of the HIV aspartic protease inhibitors ritonavir, nelfinavir, indinavir, and saquinavir, only ritonavir and saquinavir could affect Sapp1p activity (219). Another group found that ritonavir reduced Sap activity but that saquinavir did not (11). Pepstatin A, a specific aspartic proteinase inhibitor, blocks the initial penetration of *C. albicans* and *C. parapsilosis* through mucosal surfaces and reduces histopathological alterations during experimental cutaneous candidiasis (95, 249). Hence, Saps are a potential target for drug development.

Phospholipases. Phospholipases are enzymes capable of hydrolyzing one or more ester linkages in glycerophospholipids. The function of phospholipases during infection is not well understood, although it is believed that they are involved in the disruption of host membranes (101, 128). Phospholipase activity has been implicated in *C. albicans* virulence using several experimental systems. Phospholipases have been shown to affect virulence in a murine infection model, adhesion to epithelial cells (20, 58, 84), host cell penetration (222), invasion of reconstituted human oral epithelium (117, 123), and host signal transduction (87, 248).

The role of phospholipases in *C. parapsilosis* pathogenesis is less clear. There have been contradictory findings, with some investigators reporting phospholipase activity in as many as 51% of *C. parapsilosis* strains (101) and others finding no activity (128, 242, 253). Additionally, only one of four isolated *C. parapsilosis* strains causing candiduria in Sao Paulo, Brazil, exhibited phospholipase activity (59). Such inconsistencies in data could be the result of relatively small sample sizes as well as the biological differences between the tested strains. Furthermore, variations in the production of phospholipases have also been found in comparing systemic versus superficial isolates, with some investigators identifying phospholipase activity only in bloodstream isolates (58) and others describing significantly higher activities in superficial *C. parapsilosis* isolates than in systemic isolates (84).

Lipases. Lipases catalyze both the hydrolysis and synthesis of triacylglycerols and are characterized by their stability at high temperatures and in organic solvents, high enantioselectivity, and resistance to proteolysis (35). Putative roles of microbial extracellular lipases include the digestion of lipids for nutrient acquisition, adhesion to host cells and tissues, synergistic interactions with other enzymes, unspecific hydrolysis due to additional phospholipolytic activities, initiation of inflammatory processes by affecting immune cells, and self-defense mediated by lysing competing microflora (248, 264). Extracellular lipases have been proposed as potential virulence factors of bacterial pathogens, including *Staphylococcus aureus* (275), *Staphylococcus epidermidis* (161), *Propionibacterium acnes* (178), and *Pseudomonas aeruginosa* (122), as well as pathogenic fungi such as *Malassezia furfur* (226), *Hortaea werneckii* (106), and *C. albicans* (248). In *C. albicans*, 10 lipase genes have been identified (120), and we recently generated homozygous Lip8p *C. albicans* mutants to assess the affect of lipase production on disease (96). *LIP8* was selected because it is the

only lipase uniformly upregulated 4 h after infection in a systemic murine infection (264), and disruption dramatically affected virulence (96).

In *C. parapsilosis*, two lipase genes, Cp*LIP1* and Cp*LIP2*, have been identified, although only Cp*LIP2* codes for an active protein (37, 188). We have also recently explored the role of lipase in *C. parapsilosis* pathogenesis. First, we showed that lipase inhibitors significantly reduce tissue damage during *C. parapsilosis* infections of reconstituted human tissues (95). Second, we constructed Cp*LIP1*-Cp*LIP2* homozygous mutants and found that they formed thinner and less complex biofilms, had reduced growth in lipid-rich media, were more efficiently ingested and killed by macrophage-like cells, and were less virulent in infections of reconstituted human oral epithelium and a murine intraperitoneal challenge than wild-type *C. parapsilosis* organisms (97). These findings are particularly important since *C. parapsilosis* infections frequently occur in patients, often low-birth-weight neonates, receiving lipid-rich total parenteral nutrition. The recent genomic DNA sequencing project results suggest that two additional *LIP* genes may exist in *C. parapsilosis*, the expression of which under certain conditions could explain the late growth of organisms in olive oil medium or in vivo. This suggests that Cp*LIP2* and its enzyme product are potential targets for the development of antifungal drugs, particularly for patients receiving lipid emulsions.

ANTIMICROBIAL SUSCEPTIBILITY

There is currently no consensus on the treatment of invasive *C. parapsilosis* diseases, although the therapeutic approach typically includes the extraction of any removable foreign bodies and the administration of a systemic antifungal. Historically, amphotericin B has been the most frequently used antifungal. Administration of amphotericin B can be complicated by nephrotoxicity, necessitating a reduction in the drug dosage (284) or termination of therapy (181). The significant risk of potential toxicities, especially in patients with impaired renal function (15), has led to the development of lipid formulations of amphotericin B that have similar efficacy with reduced nephrotoxicity (3, 158, 201). Individual case reports documenting amphotericin B resistance in infectious strains have been published (274, 296), and studies report in vitro resistance of *C. parapsilosis* to amphotericin B at a rate of 2 to 3% (202). Documented average values of the *C. parapsilosis* MIC_{50} and MIC_{90}, obtained by various methodologies, range from 0.13 to 1 μg/ml and from 0.5 to 1 μg/ml, respectively (88, 146, 168, 175, 202, 215). Hence, although resistance has emerged among individual strains of *C. parapsilosis* during treatment, the main issue with conventional amphotericin B therapy remains the drug's poor aqueous solubility and toxicity (76).

Fluconazole is the most frequently administered alternative to amphotericin B. In vitro resistance to fluconazole has been documented among non-*C. albicans Candida* species, particularly *C. glabrata* and *C. krusei* (88, 218, 271). Additionally, there are conflicting opinions as to whether or not fluconazole use has resulted in a shift toward non-*C. albicans* species causing candidemia. While some favor the argument that it has (16), it should be noted that others conclude that azole usage has not influenced the prevalence of certain *Candida* species causing infections (244). The argument against a significant impact of azoles on resistance is based on the fact that data from various publications are confounded by the lack of standard methods for susceptibility testing and different definitions of resistance. Nevertheless, little overall variation in susceptibility to fluconazole has occurred (211), although clinical resistance in *C. parapsilosis* has been reported (246, 273). In vitro susceptibility tests have found frequencies of resistance to fluconazole ranging from 0 to 4.6% (10, 202, 212, 216, 218) and average MIC_{50} and MIC_{90} values ranging from 0.5 to 1 μg/ml and 1 to 2 μg/ml, respectively (88, 146, 168, 175, 202, 215).

Interestingly, the long-term use of fluconazole to control *C. parapsilosis* bloodstream infections in a Finland NICU eventually led to the emergence of a fluconazole-resistant strain that was responsible for cross-infections over a 12-year period (246). However, other prophylaxis studies have not identified fluconazole-resistant *C. parapsilosis*, although their durations were only 14 to 30 months (133, 135). A study including 384 infants found targeted short-course fluconazole prophylaxis for very low-birth-weight-and extremely low-birth-weight neonates to be efficacious and cost-effective (276). Of the 178 neonates on prophylaxis, only 2 (1.1%) developed invasive fungal disease due to *C. albicans* and *C. lusitaniae*, while 13 (6.3%) of the 206 infants without prophylaxis developed invasive fungal infections. Of these 13 infections, 9 (69%) were caused by *C. parapsilosis*, indicating fluconazole's effectiveness as a prophylaxis against this common neonatal pathogen. At the NICU of the Woman's Hospital of Texas, non-*C. albicans* species caused 5 (26%) of 19 cases of *Candida* infections (*C. parapsilosis* accounted for 3 infections) from 2000 to 2001, prior to the initiation of fluconazole prophylaxis (112). After the introduction of fluconazole prophylaxis, 9 (41%) of 22 cases of infection between 2002 and 2006 were caused by non-*C. albicans* species, and 6 were due to *C. parapsilosis*. Such studies have led to a broad acceptance among neonatologists of targeted prophylaxis with fluconazole for infants who are either $<$1,000 g or $\leq$27 weeks (134).

Among other azoles, in vitro resistance to itraconazole has been noted, occurring at rates of from 1.5% of *C. parapsilosis* isolates (10) to 4% (202), and voriconazole has lower MIC_{50} ($\leq$0.03 μg/ml) and MIC_{90} ($\leq$0.03 to 0.12 μg/ml) values than amphotericin B and older azoles against *C. parapsilosis* (88, 166, 168, 177, 202, 218). In vitro resistance to voriconazole is rare, with early reports showing 100% susceptibility (214). More recently, an analysis of 9,371 *C. parapsilosis* isolates showed that only 1.9% were resistant to voriconazole and that 36.7% of the fluconazole-resistant isolates were susceptible to voriconazole (212). This also shows that cross-resistance occurs for azoles. Additionally, resistance to voriconazole has developed among clinical strains previously exposed to fluconazole (182), and outbreak strains with reduced susceptibilities to both fluconazole and voriconazole have been identified (47).

Although less frequently used at present, flucytosine has been administered in combination with amphotericin B or azoles, especially in the setting of candidal meningitis (78, 255). Monotherapy is contraindicated due to the risk for the emergence of resistance, particularly during prolonged administration such as for endocarditis (113). Although a study in 1975 found an in vitro resistance rate of 23% for *C. parapsilosis*, more recent publications report flucytosine resistance rates of 2% to 6.4% (202, 223).

Echinocandins are the newest class of antifungal agents, and echinocandins currently available in the United States include caspofungin, micafungin, and anidulafungin. These drugs interfere with cell wall synthesis by inhibiting (1, 3)-β-D-glucan synthase, an enzyme that forms glucan polymers, the major component of the fungal cell wall. Caspofungin has potent antifungal activities and has been shown to be as effective as, and less toxic than, amphotericin B in the treatment of invasive candidiasis caused by *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. krusei*, *C. guilliermodii*, *C. lipolytica*, and *C. rugosa* (180, 262). However, caspofungin MICs for *C. parapsilosis* are higher than those for other *Candida* species, with average MIC_{50} and MIC_{90} values ranging between 0.85 to 2 μg/ml and 2 to 2.33 μg/ml, respectively (17, 18, 88, 146, 202). Although the basis for this resistance is not clearly understood, structural differences in the components of the cell wall, a reduced affinity for the glucan synthase protein complex, or a difference in its regulatory network may be responsible (17). This trend in susceptibility for *C. parapsilosis* extends to other echinocandin derivatives as well. For example, micafungin has an average MIC_{50} of 1 μg/ml and an average MIC_{90} of ≥2 μg/ml for *C. parapsilosis* (151, 202). Anidulafungin has an average MIC_{50} of 2 μg/ml and an average MIC_{90} of ≥2 μg/ml (168, 202, 209). Despite elevated echinocandin MIC levels, there are reports of their in vitro and in vivo activities against *C. parapsilosis* (1, 21, 68, 69, 109, 146, 200), particularly in clinical cases involving *C. parapsilosis* isolates resistant to amphotericin B, fluconazole, or both (296). Nevertheless, there are insufficient data to support a correlation between echinocandin susceptibility testing (129) and clinical outcomes, and further, there have been significant interlaboratory variations in MIC results (199). Echinocandins can fail during treatments of *C. parapsilosis* bloodstream infections in which the MICs for the echinocandin used are low (0.25 μg/ml) (46). Also, "breakthrough" infections with *C. parapsilosis* have occurred in individuals receiving echinocandins for other indications (33). In fact, at concentrations above the MIC for echinocandins, these drugs can paradoxically promote the growth of some isolates of *C. parapsilosis* and other *Candida* species in vitro (42). Additionally, recent epidemiological studies have found an association between increasing caspofungin usage and an increased incidence of *C. parapsilosis* candidemia (89). Hence, echinocandins should be used with caution during invasive *C. parapsilosis* disease.

Combination therapy with echinocandins and amphotericin B or azoles is being examined for different invasive mycoses (184). For *C. parapsilosis*, caspofungin in combination with amphotericin B can significantly improve potency in vitro and in a murine infection model (18). Clinical data detailing the effectiveness of combination therapy are rare, although a few case reports have been published. For instance, a patient with *C. parapsilosis* mural endocarditis failed monotherapy with caspofungin but recovered when treated with caspofungin and voriconazole (162).

GENETICS

Genetic and/or genomic heterogeneity is known to occur among *C. parapsilosis* isolates (32, 157, 163). The high level of genetic variation is shown in both karyotypes and DNA sequences. Moreover, data from DNA-DNA reassociation, restriction length polymorphism, and isoenzyme profiling as well as comparison of DNA sequences within the internal transcribed spacer region of the ribosomal DNA and the D1/D2 domain of the gene coding for 26S rRNA indicate that *C. parapsilosis* consists of three variant groups that may represent distinct species (148, 157, 235). Subsequent analysis of the type II DNA topoisomerase gene supports the idea that the taxon *C. parapsilosis* includes more than one species (130). Although strains from each group are found in samples from human patients, clinical isolates are predominantly of group I. There is substantial genetic variation even within group I isolates (including the type strain CBS 604/ATCC 22019). This variation is associated with several molecular determinants of virulence, such as the ability of the fungus to colonize hosts (i.e., humans or animals and skin, blood, or sputum), the appearance of specific phenotypes (i.e., antibiotic resistance), and the ability to generate biofilms (32, 217). Since the separation of the prior groups into species is recent and the vast majority of available clinical publications do not distinguish between them, this review also does not distinguish between them. As more data for the different species are collected, further differences between these species will likely accumulate.

Recently, multilocus sequence typing data provided evidence of genotypic differences between pairs of subgroups in four genes, leading to the dissociation of the former *C. parapsilosis* groups II and III to two new species, *C. orthopsilosis* and *C. metapsilosis* (267). For example, *SADH* and *SYA1* were shown to have sequence similarities of below 90% among the three species. The level of dissimilarity in the *ITS1* sequence is similar to that which supports the difference between *C. albicans* and *C. dubliniensis.*

Importantly, studies of the genetic organization of *C. parapsilosis* mitochondrial DNA reveal that most isolates possess a linear structure, in contrast to the typically circular structure as in *Saccharomyces cerevisiae*, *C. albicans*, *C. tropicalis*, and *C. orthopsilosis* isolates (239). Restriction enzyme analysis and 5′ end labeling prove that mitochondria of *C. parapsilosis* have uniform, linear DNA molecules consisting of about 30 kb, the termini of which are organized in a way similar to that for the mitochondrial telomeres of eukaryotic nuclear chromosomes (143, 192). Analyses of the molecular architecture and genetic organization of mitochondrial genomes in representative strains from all three genotype groups of *C. parapsilosis* (now *C. parapsilosis*, *C. orthopsilosis*, and *C. metapsilosis*) (239) provide the basis for analyzing the biodiversity of clinical isolates and for the development of species- as well as group-specific molecular probes targeting mitochondrial DNA sequences (194). Sequence analysis reveals that the linear mitochondrial genome is highly compact, carrying genes for 14 protein subunits of the respiratory chain complexes and ATP synthase, rRNAs of the large and small subunits of the mitochondrial ribosome, and 24 tRNAs (193). Additionally, although structurally diverse, the coding sequences of the mitochondrial DNA of *C. parapsilosis* are highly similar to those of *C. albicans*. In contrast, a genome survey of partial DNA sequence information for over 3,900 potential genes shows that the average sequence identity between *C. parapsilosis* and *C. albicans* is only 59% (160).

C. parapsilosis lacks nucleotide sequence diversity (267). The frequency of mutation in *C. albicans* is about 1/140 bp in

examined coding regions (55, 268). In contrast, studies of *C. parapsilosis* find only two polymorphic nucleotide sites among 7.5-kb sequences (267) and only four mutations among more than 36 kb (91). The lack of nucleotide sequence diversity suggests that *C. parapsilosis* is highly clonal and has only recently, within the past one million years, emerged as a species. Interestingly, although *C. parapsilosis* isolates essentially lack DNA sequence variability, the relatively high level of genetic heterogeneity among *C. orthopsilosis* isolates suggests that *C. parapsilosis* might have evolved from this species (267). The evidence of occasional heterozygosities in *C. parapsilosis* gene sequences suggests that *C. parapsilosis* is predominantly aneuploid rather than haploid or diploid (91). Additional evidence pointing toward the aneuploidy of *C. parapsilosis* is the variation from 168 units to 258 units (mean = 208) in *C. parapsilosis* strain nuclear size, which is about one-half of the nuclear size of *C. albicans*, a known diploid (91).

C. metapsilosis (formerly *C. parapsilosis* group III) is very rarely isolated from clinical samples (139). Additionally, the species is less virulent in tissue culture models than *C. parapsilosis* or *C. orthopsilosis* (95). The currently available data suggest that *C. metapsilosis* is an environmental organism, whereas *C. parapsilosis* and *C. orthopsilosis* evolved by adaptation to mammalian niches (267). There are insufficient data to determine where *C. metapsilosis* fits into the evolution of the three species.

Molecular Manipulations

Molecular genetic studies of *C. parapsilosis* had been hindered by the aneuploidy of the organism (91) and the lack of a characterized sexual cycle. Furthermore, until 2007 an efficient method for targeted gene disruption to generate mutants for the identification of *C. parapsilosis* virulence factors did not exist. A transformation system based on the complementation of a galactokinase-deficient mutant of *C. parapsilosis* by the homologous gene (*GAL1*) was described in 2002, but it could not be used to target genes in prototrophic wild-type strains (191). We previously showed that the dominant selection marker MPA^R can be used for *C. parapsilosis* transformation (94), and we created an improved system for efficient gene deletion based on the repeated use of the dominant nourseothricin (Nou) resistance marker (Ca*SAT1*) and its subsequent deletion by site-specific recombination (97) as previously described for *C. albicans* (227). The proof of principle for the generation of homozygous *C. parapsilosis* mutants was the production of *C. parapsilosis LIP1* and *LIP2* knockout mutants (97). The Nou selection protocol had several advantages, including rapid growth of transformants, fewer spontaneously resistant colonies, and a higher recombination efficiency. The method described is the first detailing the generation of *C. parapsilosis* mutants that differ from the parental strain only by the absence of a target gene, a useful tool for future investigations of significant virulence factors. The efficiency of the method has also been demonstrated by an independent group who generated *URA3* and *BCR1* knockout mutants (71).

CONCLUSIONS

The emergence of *C. parapsilosis* as the leading non-*C. albicans Candida* species poses a major threat for the future, and unfortunately, the incidence of *C. parapsilosis* infections may continue to rise. For instance, advances in health care will allow for even higher survival rates among neonates in NICUs, and the increased use of immunomodulatory medications for diverse indications (i.e., autoimmune diseases, cancer, infectious diseases, etc.) will place more people at risk of infection with *C. parapsilosis*. This pathogen has a high affinity for parenteral nutrition, frequently colonizes the hands of health care workers, and forms biofilm on prosthetic surfaces and central venous catheters. Its recognition as a major cause of numerous diseases across the globe, particularly among neonates and in hospital environments, merits additional investigations concerning its epidemiology, microbiology, genetics, and antimicrobial susceptibility. Given the incidence of disease and the unacceptably high morbidity and mortality associated with *C. parapsilosis*, there is an urgent need for more effective therapeutics. For this, additional genetic studies are necessary to identify *C. parapsilosis* virulence factors that can be targeted by antimicrobial agents to control disease.

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