Candida parapsilosis: Epidemiology, Pathogenicity, Clinical Manifestations, and Antimicrobial Susceptibility

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Early reports associated *Candida parapsilosis* with endocarditis in intravenous narcotic addicts. More recently, this species has emerged as an important nosocomial pathogen, with clinical manifestations including fungemia, endocarditis, endophthalmitis, septic arthritis, and peritonitis, all of which usually occur in association with invasive procedures or prosthetic devices. Outbreaks of *C. parapsilosis* infections have been caused by contamination of hyperalimentation solutions, intravascular pressure monitoring devices, and ophthalmic irrigating solution. Experimental studies have generally shown that *C. parapsilosis* is less virulent than *Candida albicans* or *Candida tropicalis*. However, characteristics of *C. parapsilosis* that may relate to its increasing occurrence in nosocomial settings include frequent colonization of the skin, particularly the subungual space, and an ability to proliferate in glucose-containing solutions, with a resultant increase in adherence to synthetic materials. Recently developed molecular techniques may facilitate the continued exploration of the epidemiology and pathogenesis of *C. parapsilosis* infections.

As techniques for the speciation of yeasts become standard in most clinical microbiology laboratories [1] and molecular typing methods are applied to these organisms [2, 3], important mycologic, clinical, and epidemiological differences between *Candida albicans* and other *Candida* species are being defined. Recent national data indicate that more than 30% of nosocomial candidal infections are now due to species other than *C. albicans* [4].

The original description of *Candida parapsilosis* is attributed to Ashford, who in 1928 reported the isolation from stool of a species of *Monilia* that failed to ferment maltose [5]. He used the term *parapsilosis* to distinguish such strains from the more frequent isolate *Monilia psilosis*, which was later designated *Candida albicans*. *C. parapsilosis* was considered nonpathogenic until 1940, when it was reported as the cause of a fatal case of endocarditis in a narcotic addict [6, 7]. Early investigators suspected that exogenous introduction of this organism by intravenous injection was important in the development of invasive infection. This hypothesis was remarkably predictive of the future role of *C. parapsilosis* in infections associated with invasive devices and parenteral solutions.

This paper is the result of a comprehensive review of the literature on *C. parapsilosis*, with an emphasis on the features that distinguish this species from other members of the genus.

Received 14 June 1991; revised 5 September 1991.

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Clinical Infectious Diseases 1992;14:756–66

1058-4838/92/1403-0034$02.00

Methods

A search of the literature for all citations including the terms *Candida parapsilosis* and *Candida parakrusei* (a former designation for the same species) was performed on the MEDLINE (MEDLARS II) system for the period 1968–1990. An additional search was undertaken for 1970–1985 on the BIOSIS system. The bibliographies of selected articles were used to identify relevant articles published before 1968.

Results

Prevalence

As opposed to *C. albicans* and *Candida tropicalis*, which are considered obligate human parasites, *C. parapsilosis* has a somewhat wider distribution in nature and has been isolated from a variety of nonhuman sources [8–11]. It can, however, be part of the normal flora of the human skin [12, 13]. McGinley et al. found *C. parapsilosis* to be the fungus most frequently isolated from the subungual space of healthy volunteers [14]. Although *C. albicans* is clearly the predominant species of *Candida* colonizing the gastrointestinal and genital mucosae, *C. parapsilosis* has been recovered from stool in the presence of malnutrition [15], has been isolated infrequently from the oropharynx of healthy neonates [16] and asymptomatic diabetics [17], and has accounted for fewer than 10% of candidal isolates from the female genitourinary tract [18–20].

Various studies have evaluated *C. parapsilosis* in hospitalized patients. This species was found once among 202 strains of *Candida* isolated from all sites from 151 patients at Boston City Hospital in 1969 and 1970 [21] and comprised 9.4% of 530 *Candida* isolates from patients at the Mayo Clinic in

Table 1. Prevalence, frequency of dissemination, and mortality in *C. parapsilosis* fungemia.

Period [reference]	Population	Prevalence of *C. parapsilosis* fungemia*	Frequency of disseminated infection†	Mortality (%) with indicated *Candida* species		
				C. parapsilosis	*C. albicans*	*C. tropicalis*
1962–1972 [27]	National Cancer Institute	7/70 (10)	1/34 (2.9)	. . .	. . .	. . .
1971–1975 [25]	Pittsburgh Veterans Administration Hospital	12/45 (26.7)	. . .	. . .	. . .	. . .
1972–1977 [28]	Cincinnati General Hospital	3/85 (3.5)	. . .	. . .	. . .	. . .
1972–1981 [29]	Mayo Clinic	29/302 (9.6)	. . .	. . .	. . .	. . .
1974–1977 [30]	Memorial–Sloan Kettering Cancer Center	16/136 (11.8)	0/44 (. . .)	23	83	92
1978–1982 [31]	Memorial–Sloan Kettering Cancer Center	23/200 (11.5)	0/53 (. . .)	30	79	78
1975–1977 [32]	University of Colorado Hospitals	7/51 (13.7)	. . .	. . .	. . .	. . .
1976–1980 [33]	M. D. Anderson Cancer Hospital	7/235 (3.0)	3/133 (2.3)	. . .	. . .	. . .
1976–1983 [34]	University of Louisville Hospitals	22/83 (26.5)	. . .	32	58	55
1981–1985 [35]	Western Reserve Care System	7/48 (14.6)	. . .	. . .	. . .	. . .
1983–1986 [36]	Harper Hosptial (Detroit)	16/135 (11.9)	. . .	44	60	59

* Number of cases of *C. parapsilosis* fungemia/total number of cases of fungemia (percentage of cases involving *C. parapsilosis*).
† Number of cases of disseminated *C. parapsilosis* infection/total number of autopsies on patients with fungemia (percentage of autopsies in which disseminated *C. parapsilosis* infection was documented).

1971 [22]. Among infants of very low birth weight in a neonatal intensive care unit, 5% were colonized with *C. parapsilosis*—a rate of occurrence that represented 18% of all colonizing strains of *Candida* [23]. Of pediatric burn patients at one institution, 11% were colonized with *C. parapsilosis* [24]. The authors of several studies have noted a relatively high prevalence of this fungus among blood isolates. In 1978 Mayrer et al. observed that, although only 8% of yeast isolates at the Pittsburgh Veterans Administration Hospital were *C. parapsilosis*, this species accounted for 27% of *Candida* isolates from blood and for 17% of those from intravenous catheters [25]. Kiehn and colleagues reported that *C. parapsilosis* made up only 3.7% of 3,340 yeast isolates from all sites as opposed to 30% of isolates from blood [26]. Overall, *C. parapsilosis* has accounted for 3%–27% of cases of fungemia in large hospital-based studies (table 1), although in outbreaks (see below) its prevalence among blood isolates has been as high as 51% [37].

Pathogenicity

Most experimental studies have indicated that the virulence of *C. parapsilosis* is limited compared with that of *C. albicans* and *C. tropicalis*. *C. parapsilosis*, when injected intravenously, was lethal to mice with experimentally induced diabetes but not to healthy mice [38]. *C. albicans* and *C. tropicalis* were lethal to both healthy and diabetic mice at doses significantly lower than the lethal doses for *C. parapsilosis*. Cyclophosphamide-induced immunosuppression did not render mice susceptible to intravenous challenge with *C. parapsilosis* [39]. However, the fungus caused renal abscesses (but not death) after being injected intravenously into cortisone-treated mice [40] and disseminated to visceral organs after being administered intragastrically to antibiotic-treated mice [41].

Higher inocula of *C. parapsilosis* than of *C. albicans* or *C. tropicalis* were required to induce lesions on the chick chorioallantoic membrane [42]. In a model using keratinized rat-tongue mucosa, *C. parapsilosis* showed less ability to invade tissue than did *C. albicans* or *C. tropicalis* [43]. Moreover, *C. parapsilosis* adhered less markedly than the other two species to vaginal and buccal epithelial cells [44], vascular endothelial cells [45], and fibrin clots [46]. However, isolates of *C. parapsilosis* from patients with vaginitis have been reported to secrete greater amounts of an acid proteinase and to be more pathogenic in an animal model than vaginal isolates from asymptomatic patients [47]. Further, some evidence suggests that under certain environmental conditions the growth characteristics of *C. parapsilosis* may be altered in a manner that increases virulence. The adherence of *C. parapsilosis* to acrylic was markedly enhanced and was greater than that of *C. albicans* after growth in a 50 m*M* glucose solution [48]. In addition, *C. parapsilosis* was shown to have a selective growth advantage in certain hyperalimentation solutions [49].

Although their implications have not been explored systematically in vivo, these observations could be important clinically, given the strong association between *C. parapsilosis* infections and both hyperalimentation and prosthetic devices. Marrie and Costerton used scanning and transmission electron microscopy to examine a catheter removed from a patient receiving hyperalimentation therapy and noted the presence of *C. parapsilosis* in an extensive biofilm associated with a fibrous material on the plastic surface [50]. In another

study five prosthetic heart valves removed from patients with endocarditis due to *C. parapsilosis* were examined. Candidal cells were noted in an intracellular fibrillar matrix [51]. The role of biofilms in the adherence of other organisms, such as coagulase-negative staphylococci, has been demonstrated [52].

Clinical Manifestations

Fungemia. Studies of fungemia that have yielded comparative data on species including *C. parapsilosis* are summarized in table 1. Meunier-Carpentier studied the features of fungemia due to the seven most frequently isolated species of yeast among 110 patients at Memorial–Sloan Kettering Cancer Center in New York between 1974 and 1977 [30]. A number of important observations regarding *C. parapsilosis* were made in this study. First, there was a strong association between the isolation of *C. parapsilosis* from the blood and parenteral hyperalimentation. Ten (77%) of 13 patients with *C. parapsilosis* fungemia but only 18 (19%) of 97 patients with other yeast species in the bloodstream had received hyperalimentation. Second, mortality was lower (23%) among patients with *C. parapsilosis* fungemia than among those whose bloodstream was infected with other species. Finally, as opposed to other yeast species, *C. parapsilosis* infecting the blood was not associated with prior colonization at other sites; this fact suggested direct vascular introduction of the organism.

A lower mortality associated with *C. parapsilosis* fungemia than with bloodstream infection due to other *Candida* species has been confirmed in various studies. In an investigation of 200 episodes of fungemia at Memorial–Sloan Kettering in 1978–1982, Horn et al. reported a mortality of 30% among patients with *C. parapsilosis*, 79% among those with *C. albicans*, 78% among those with *C. tropicalis*, and 68% among those with *Candida glabrata* [31]. Dyess reported mortality figures of 32% among patients with *C. parapsilosis* fungemia, 58% among those with *C. albicans* fungemia, and 55% among those with *C. tropicalis* fungemia [34]. At Harper Hospital in Detroit, Komshian and associates documented a mortality of 44% for *C. parapsilosis* fungemia—the lowest rate for any *Candida* species [36]. In line with this lower mortality, *C. parapsilosis* accounts for a smaller percentage of cases of disseminated candidiasis documented at autopsy [27, 30, 31, 33]. These data are consistent with experimental studies showing a lesser degree of tissue invasion by *C. parapsilosis* than by other *Candida* species after intravenous challenge. However, as will be discussed below, both tissue invasion and death are more frequent in cases of *C. parapsilosis* endocarditis than in primary *C. parapsilosis* fungemia.

Soon after its introduction, parenteral hyperalimentation was recognized as a risk factor for candidemia [53], and it was subsequently associated more specifically with bloodstream infection by *C. parapsilosis* [30, 37, 54–57]. This association was further defined in investigations of nosocomial outbreaks of *C. parapsilosis* fungemia. In 1977 Plouffe et al. described 22 cases of *C. parapsilosis* fungemia over a 4-month period among postoperative patients and patients with burns [55]. Epidemiological investigation revealed that albumin and hyperalimentation solutions had been contaminated during their preparation in a vacuum pump system. This contamination resulted from backflow when the container of prepared solution was not disconnected from the system before the vacuum pump was turned off. Contamination of the vacuum pump with *C. parapsilosis* was documented, as was support of the growth of the organism by hyperalimentation and albumin solutions.

Solomon et al. also identified a contaminated vacuum-pump system that had been used to add albumin to hyperalimentation solutions as the cause of a cluster of five cases of *C. parapsilosis* fungemia [56]. In addition, two outbreaks of *C. parapsilosis* fungemia among infants in neonatal intensive care units were described [37, 57]. These cases were epidemiologically associated with hyperalimentation as well as with intravascular pressure monitoring devices used on catheters through which hyperalimentation was often administered. Although contamination during the preparation of hyperalimentation solutions was not detected, *C. parapsilosis* was recovered in both outbreaks from the surfaces of the pressure transducers, and the outbreaks ceased when the pressure transducers were appropriately processed with high-level disinfection between uses.

The frequency with which epidemic *C. parapsilosis* fungemia has been associated with contaminated medical devices suggests that such exogenous sources should be sought in epidemiological investigations of clusters of cases. Additional reports have documented *C. parapsilosis* fungemia among patients in other clinical settings, including individuals on a burn unit [58], severely ill postoperative patients [59], a patient without identified risk factors [60], and a patient with a necrotic nasal ulcer associated with an oxygen cannula [61].

Endocarditis. As has been mentioned, endocarditis was the first documented infection due to *C. parapsilosis* [6]. Despite experimental evidence indicating its limited virulence compared with other candidal species, *C. parapsilosis* has accounted for a significant proportion of reported cases of fungal endocarditis, particularly among intravenous drug users [62]. In fact, the first three reported cases of fungal endocarditis were in heroin addicts and were due to *C. parapsilosis* [6, 63, 64]. There was some speculation that this cluster of cases around 1940 was due to widespread distribution of a contaminated lot of heroin. Joachim and Polayes isolated the organism from the container from which their patient injected drugs [6], but a more systematic culture survey of confiscated narcotic samples at the time failed to reveal the fungus [63]. It is interesting that, 40 years later, Brandstetter and Brause reported isolation of the organism from the syringes

Table 2. Clinical characteristics of 56 reported cases of endocarditis due to *C. parapsilosis*.

Characteristic	No. (%) of cases
Age (y)*	
<1	1 (2)
1–20	4 (7)
21–50	36 (64)
>50	12 (21)
Male gender	42 (75)
Intravenous narcotic use	25 (46)
Preexistent valvular heart disease	33 (60)
Previous episode of endocarditis	11 (18)
Previous cardiac surgery	24 (44)
Valvulotomy/commissurotomy	6 (11)
Valve replacement	18 (33)
Valve type	
Native	39 (70)
Prosthetic	17 (30)
Valve(s) infected†	
Aortic	28 (50)
Mitral	17 (30)
Aortic and mitral	3 (5)
Tricuspid	3 (5)

* Not specified in three cases.
† Not specified in four cases; one case involved an atrial myxoma.

used by an addict with *C. parapsilosis* endocarditis and postulated that the cleaning of the drug paraphernalia with a glucose-containing alcoholic beverage may have fostered the growth of *C. parapsilosis* [65].

In all, reports of 56 cases of *C. parapsilosis* endocarditis were identified [6, 7, 62–96], the features of which are summarized in table 2. Nearly 50% of the patients involved had a history of narcotic addiction, and 60% had preexistent valvular disease; overall, 89% of cases had one of these two predisposing factors. Forty-four percent of patients had undergone previous open heart surgery. Of 52 cases with available data, 28 involved the aortic valve, 17 the mitral valve, 3 both the aortic and mitral valves, and 3 the tricuspid valve; the remaining case occurred in association with a left atrial myxoma. Thirty percent of cases involved prosthetic valves. Of 27 cases for which autopsy data were reported, 44% involved visceral organs and major vessel emboli.

The treatment and outcome of the cases of endocarditis are summarized in table 3. Overall, the rate of survival was ~35%, but that among patients treated medically was only 22%, and no patients given only supportive care survived. In cases reported since 1970, a combined medical/surgical approach has been the rule and has resulted in an increase in the survival rate to 50%–64%, although follow-up on some of these cases has been limited and late recurrences with some deaths have been documented. Medical cure of prosthetic valve endocarditis due to *C. parapsilosis* has not been reported.

These data suggest that the establishment of endocardial infection is critical in the pathogenesis of *C. parapsilosis* infection. When *C. parapsilosis* fungemia occurs in the setting of endocarditis, the mortality rate and frequency of dissemination are similar to those associated with *C. albicans* fungemia, whereas these figures are much lower than those for primary (catheter-associated) *C. parapsilosis* fungemia.

Infections of the nails and skin. In addition to being a frequent isolate from the healthy subungual space and other cutaneous sites, *C. parapsilosis* is very commonly isolated from pathological lesions of the nails and skin. Reiersol noted that *C. parapsilosis* accounted for 21 of 40 yeasts isolated from diseased skin and nails of 131 patients [97]. Similarly, Zaias et al. found that *C. parapsilosis* made up 43 of 60 yeasts isolated from the diseased nails of 183 patients [98]. The organism is most often found in association with the distal subungual type of onychomycosis [99]. In a large culture survey of dermatologic specimens, Dion and Kapica found *C. parapsilosis* in 48% of the specimens from which any yeast was isolated [100]. Further, *C. parapsilosis* was the yeast most commonly isolated from mixed infections in association with pathogenic dermatophytes.

English et al. reported that *C. parapsilosis* was frequently isolated from the venous leg ulcers of patients, although in pathogenic role in these cases was in doubt and some evidence indicated nosocomial transmission in one clinic in which occlusive bandages were applied [101]. Facial and pubic folliculitis due to *C. parapsilosis* has also been described [102, 103].

Despite its common isolation from the skin, *C. parapsilosis* has not been associated with chronic mucocutaneous candidiasis. Perhaps the immune defect in patients with the latter infection is specific for *C. albicans* [104].

Ocular infections. The most important ocular manifestation of *C. parapsilosis* infection has been postoperative endophthalmitis. This infection was first reported by Rosen and Friedman; the case described followed cataract extraction [105]. The diagnosis was proven by anterior chamber aspiration and culture, and treatment included antifungal drops as well as subtenonian (under Tenon's capsule) injections of amphotericin B, which resulted in recovery of vision. Before diagnosis, this patient had received corticosteroid eye drops.

Gilbert and Novak reported a case of *C. parapsilosis* endophthalmitis following extracapsular cataract extraction and intraocular lens implantation [106]. This case was treated with vitrectomy and intracameral amphotericin B as well as topical and intravenous amphotericin B and oral flucytosine, with partial return of visual acuity and preservation of the intraocular lens. The patient had received topical and subtenonian steroids for several weeks before diagnosis.

Stransky reported a case of postoperative endophthalmitis due to *C. parapsilosis* in a 79-year-old diabetic woman after intracapsular cataract extraction [107]. This patient was

Table 3. Survival of patients with endocarditis due to *C. parapsilosis*, by type of treatment.

Treatment	No. of survivors/no. of cases (% of patients surviving)*		
	NVE	PVE	Total
Supportive	0/6 (. . .)	0/1 (. . .)	0/7 (. . .)
Medical	5/16 (31)	0/7 (. . .)	5/23 (22)
Medical/surgical	8–10†/15 (53–67)	3–4‡/7 (43–57)	11–14/22 (50–64)
Total	13–15/37 (35–41)	3–4/15 (20–27)	16–19/52 (31–37)

* NVE = native valve endocarditis; PVE = prosthetic valve endocarditis.
† Two patients experienced a relapse (at 12 and 13 months, respectively) and died.
‡ One patient experienced a relapse at 3 months; the outcome was not stated.

treated postoperatively with topical steroids, and the diagnosis was eventually confirmed by vitrectomy. In addition to undergoing the latter procedure, this woman received intravitreal injections of amphotericin B and dexamethasone. She was also treated briefly with systemic flucytosine, but the infecting organism was resistant to this agent.

In 1983 a widespread outbreak of postoperative endophthalmitis following cataract extraction and intraocular lens implantation was traced to intrinsic contamination (during manufacture) of a lot of balanced basic salt eye-irrigating solution [108–110]. This outbreak involved approximately 30 patients in four states. Most cases were treated with vitrectomy and intraocular amphotericin B; a significant number ended in residual decreased visual acuity, but no patient had a complete loss of vision.

In contrast to postoperative infections, hematogenous endophthalmitis secondary to *C. parapsilosis* fungemia appears to be rare [111]. Studies at autopsy have not shown *C. parapsilosis* at ocular sites, and, in an experimental model of hematogenous endophthalmitis in rabbits, this organism was unable to establish ocular infection after intravenous injection [112].

Corneal ulceration due to *C. parapsilosis* has been described in a patient receiving antibiotic and steroid therapy [113]. In addition, apparent conjunctival colonization or superinfection by *C. parapsilosis* was described during an epidemic of keratoconjunctivitis caused by adenovirus at a Vietnamese refugee camp [114].

Arthritis. Eight cases of infectious arthritis due to *C. parapsilosis* have been described (table 4). All cases were monoarticular, and seven involved a large joint, i.e., knee, hip, or shoulder. Seven cases were preceded by instrumentation of the joint involving placement of a joint prosthesis, joint injection, or arthrocentesis. The only case not preceded by direct joint invasion occurred in an intravenous drug user who gave a history of "skin popping" near the shoulder joint in which septic arthritis due to *C. parapsilosis* subsequently developed.

Systemically administered amphotericin B, sometimes with flucytosine, appeared to be the most successful medical regimen for the treatment of these infections. One case apparently had a favorable outcome when treated with ketoconazole in association with surgical drainage, although long-term follow-up was not reported. In all four cases of prosthetic infection, removal of the prosthesis was required for resolution of the infection. In one of these cases, a second prosthesis was successfully implanted 1 year after infection, without recurrence.

It is noteworthy that more than half of cases of candidal infection following prosthetic arthroplasty have been due to species other than *C. albicans* [123]. Arthritis caused by the latter organism has been described more commonly in the setting of hematogenous joint invasion complicating disseminated candidiasis and is more commonly polyarticular [124].

Peritonitis. The majority of reported cases of peritonitis due to *C. parapsilosis* have involved patients undergoing peritoneal dialysis, particularly continuous ambulatory peritoneal dialysis (CAPD) [125–127]. The remainder of cases have followed intraperitoneal surgery, often with intestinal perforation or peritoneal lavage. Bayer et al. reviewed the literature on candidal peritonitis in 1976 and found 10 cases complicating peritoneal dialysis (none of which were due to *C. parapsilosis*) and 12 cases following gastrointestinal surgery or perforation (one of which was caused by *C. parapsilosis*) [128].

Eisenberg and colleagues reported 11 cases of fungal peritonitis in patients undergoing peritoneal dialysis at a single center from 1980 to 1983, two of which were due to *C. parapsilosis*. In reviewing the literature for 1966–1984, these authors found another five cases of peritonitis due to *C. parapsilosis* among 77 cases in patients receiving peritoneal dialysis; *C. albicans* was a much more common pathogen in these cases, being isolated in 34 instances [129].

However, in a recent series of 17 cases of fungal peritonitis in patients receiving chronic peritoneal dialysis, *C. parapsilosis* was the most common pathogen, accounting for six cases [130]. Most cases involved patients who had had multiple previous episodes of bacterial peritonitis treated with intraperitoneal and systemic antibacterial agents. Five of these patients received intraperitoneal amphotericin B alone or in combination with systemic amphotericin B. Results of therapy in this group were generally unsatisfactory, with no pa-

Table 4. Clinical features of patients with arthritis due to *C. parapsilosis*.

Case [reference]	Year	Age (y)/ gender of patient	Joint*	Associated condition(s)	Previous arthrocentesis, joint injections	Intraarticular steroid treatment	Therapy†		Outcome
							Medical	Surgical	
1 [115]	1973	75/F	Knee	DJD‡	Yes	Yes	Intraarticular AmB, 5FC	. . .	Relapse
							AmB (335 mg), 5FC × 4 mo		Resolution
2 [116]	1976	50/M	Shoulder	Heroin addiction, "skin popping" near joint	No	No	5FC × 1 mo	. . .	No improvement
							AmB (975 mg)		Resolution
3 [117]	1976	64/M	Knee (P)	Rheumatoid arthritis, treatment with steroids and cyclophosphamide for preceding 2 mo	Yes	Yes	AmB (450 mg), 5FC × 3 mo		No improvement
							AmB + 5FC 1 w preoperatively, 4 w postoperatively; 5FC × additional 2 mo	Prosthesis removal, knee fusion	Resolution
4 [118]	1980	75/F	Hip (P)	DJD	No	No	AmB (1 g), 5FC × 2 w	Prosthesis removal; reimplantation 1 y later	Resolution
5 [119]	1980	57/M	Knee	Polycystic kidney disease, hemodialysis	Yes	Yes	Intraarticular AmB, AmB (119 mg)	. . .	No improvement; refusal of further treatment
6 [120]	1981	59/M	Shoulder (P)	DJD, heroin addiction	No	No	Postoperative AmB (2 g), then ketoconazole	Prosthesis removal	Resolution
7 [121]	1984	45/M	Wrist	Polycystic kidney disease, hemodialysis; previous wrist exploration, synovectomy	Yes	Yes	Ketoconazole	Drainage	Negative postoperative cultures; no long-term follow-up
8 [122]	1986	35/M	Knee (P)	DJD	?	?	5FC postoperatively	Prosthesis removal	Not stated

* (P) indicates a prosthetic joint.
† AmB = amphotericin B (administered intravenously unless otherwise stated); 5FC = flucytosine.
‡ DJD = degenerative joint disease.

tient continuing to receive peritoneal dialysis over the long term despite microbiological cure in some instances. A significant proportion of the patients given intraperitoneal amphotericin B had abdominal pain, and an occasional patient developed intraperitoneal adhesions.

The recommendations of the authors of this study for therapy in such cases included continuous intraperitoneal lavage with miconazole and oral administration of ketoconazole, followed by catheter replacement and ketoconazole therapy for another 4–6 weeks. With the advent of additional imidazole and triazole agents, the optimal management of CAPD-associated peritonitis due to *C. parapsilosis* is uncertain. Isolated reports indicate successful therapy with these agents without removal of the catheter [131], but, until further data confirm the efficacy of this approach, catheter removal should remain an important part of the management of dialysis-associated peritonitis due to *C. parapsilosis*.

Other infections. Infections of the CNS with *C. parapsilosis* have been extremely rare. Lipton et al. reported a case of *C. parapsilosis* endocarditis in a drug addict with multiple cerebral mycotic aneurysms and subsequent subarachnoid hemorrhage [132]. The only reported case of meningitis due to *C. parapsilosis* was in a 560-g neonate who also had *C. parapsilosis* fungemia and had been treated with parenteral hyperalimentation [133]. The organism was eradicated by amphotericin B plus flucytosine, but the patient later died of other causes. Only a very slight cellular response was seen in the CSF during the infection.

In line with its low prevalence on gastrointestinal and genital mucosal surfaces, *C. parapsilosis* is an infrequent cause of vulvovaginitis [134] and has been isolated from only a few cases of oral candidiasis [135, 136]. Hematogenous renal lesions have been described in patients with *C. parapsilosis* endocarditis [137], but few data have been published on the

frequency of primary urinary tract infection due to *C. parapsilosis.*

Other reported clinical manifestations of infections with *C. parapsilosis* include septic abortion associated with an intrauterine device [138] and gangrenous cholecystitis associated with fungemia in a patient receiving parenteral hyperalimentation [139].

Antimicrobial Susceptibility

Information on the antimicrobial susceptibility of *C. parapsilosis* (like that on the susceptibility of other fungi) is limited by a lack of standardization of methods as well as by a lack of data on the relation between in vitro and in vivo activity. *C. parapsilosis* is generally susceptible to ≤ 0.2 μg of amphotericin B/mL [140]. Seidenfeld et al. have, however, reported tolerance to amphotericin B in *C. parapsilosis*, with minimal fungicidal concentrations more than 32-fold higher than the MIC [141]. The in vivo significance of this finding is unknown. Additive as well as synergistic interactions of the combination of amphotericin B and rifampin have been reported [142–144]. Development of resistance to flucytosine has been well described in a number of fungal species and has been reported in 23% of strains of *C. parapsilosis* studied experimentally [145]. In addition, the emergence of resistance to flucytosine in *C. parapsilosis* has been documented clinically during therapy for endocarditis [87]. In this case resistance was shown to be due to loss of cytosine deaminase activity. *C. parapsilosis* has generally shown susceptibility to imidazole agents, including clotrimazole, bifonazole [146], miconazole, and ketoconazole [147], as well as to the newer triazole compounds, including itraconazole [148], saperconazole [149], and terconazole [150]. In a rabbit model fluconazole was reported to be effective in the eradication and prevention of *C. parapsilosis* endocarditis [151]. Treatment with fluconazole resulted in microbiological cure of two cases of *C. parapsilosis* fungemia in immunocompromised children, although a dosage of 12 mg/(kg · d) was required [152]. Cultures of blood from a cancer patient with catheter-related *C. parapsilosis* fungemia became sterile with catheter removal and a 13-day course of fluconazole [153].

It is noteworthy that the lipopeptide antifungal agent cilofungin (LY121019) has shown consistently poor activity against *C. parapsilosis* [154–161], although a related compound (L671,329) has exhibited good activity against this species [162]. Other compounds showing in vitro activity against *C. parapsilosis* include the allylamine SF86-327 [163], chlorpromazine [164], and difluoromethylornithine (DFMO) [165].

Typing Methods

Various methods of strain delineation have been applied to *Candida* species for the purpose of studying their pathogenesis and epidemiology. Previously, the only available methods were those based on phenotypic characteristics; as molecular techniques have been developed in eukaryotes, however, data on genotypic analysis of *Candida* species have emerged. Most work so far has involved *C. albicans*, and this research has recently been reviewed [166]. However, molecular methods, including restriction enzyme analysis of whole-cell [2] and mitochondrial DNA [167] as well as gene probing [168], have now been applied to non-*albicans* species, including *C. parapsilosis.* The differentiation of strains of *C. parapsilosis* by electrophoretic karyotyping using rotating-field gel electrophoresis or contour-clamped homogeneous-field electrophoresis (CHEF) has recently been reported [169]. In the latter study electrophoretic karyotyping was superior to restriction enzyme analysis in differentiating environmental from clinical isolates. An additional preliminary report appears to confirm the usefulness of CHEF in discriminating among clinical strains of *C. parapsilosis* [170].

Conclusions

The epidemiology, clinical manifestations, and antimicrobial susceptibility of *C. parapsilosis* have been reviewed. Early reports associated this species with endocarditis in narcotic addicts, but more recently it has emerged as an important nosocomial pathogen.

The most common clinical manifestation of *C. parapsilosis* is intravascular infection—either fungemia associated with parenteral hyperalimentation and intravascular catheterization or endocarditis in patients with a history of intravenous drug use or cardiac surgery. Catheter-associated *C. parapsilosis* fungemia has infrequently led to the establishment of disseminated infection and has been associated with lower mortality than that documented for bloodstream infection with *C. albicans* or *C. tropicalis.* Endocarditis due to *C. parapsilosis*, on the other hand, is commonly complicated by visceral dissemination and is associated with a mortality comparable to that for deep *C. albicans* infection. Other focal infections due to *C. parapsilosis* include endophthalmitis, peritonitis, and arthritis, all of which are usually related to invasive procedures, prosthetic devices, or contaminated solutions. In addition, *C. parapsilosis* colonizes and infects human nail beds more frequently than other *Candida* species.

Several factors may give *C. parapsilosis* a selective advantage in the modern medical environment, including proliferation in high concentrations of glucose, adherence to prosthetic materials, colonization of human hands, and possibly resistance to new antifungal agents. Through the application of newer methods of molecular typing to the study of *C. parapsilosis* infection, our understanding of the epidemiology of this important nosocomial pathogen should be enhanced in the near future.

Acknowledgments

The author thanks Dr. Michael M. McNeil for review of the manuscript; Lynn B. Morrell and Irene Cason-Tucker for secretarial assistance; and Drs. Steven L. Solomon, William R. Jarvis, and William J. Martone for supervision.

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