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Epidemiology and Outcomes of Candidemia in 2019 Patients: Data from the Prospective Antifungal Therapy Alliance Registry

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Background. Candidemia remains a major cause of morbidity and mortality in the health care setting, and the epidemiology of *Candida* infection is changing.

Methods. Clinical data from patients with candidemia were extracted from the Prospective Antifungal Therapy (PATH) Alliance database, a comprehensive registry that collects information regarding invasive fungal infections. A total of 2019 patients, enrolled from 1 July 2004 through 5 March 2008, were identified. Data regarding the candidemia episode were analyzed, including the specific fungal species and patient survival at 12 weeks after diagnosis.

Results. The incidence of candidemia caused by non-*Candida albicans* *Candida* species (54.4%) was higher than the incidence of candidemia caused by *C. albicans* (45.6%). The overall, crude 12-week mortality rate was 35.2%. Patients with *Candida parapsilosis* candidemia had the lowest mortality rate (23.7%; $P < .001$) and were less likely to be neutropenic (5.1%; $P < .001$) and to receive corticosteroids (33.5%; $P < .001$) or other immunosuppressive drugs (7.9%; $P = .002$), compared with patients infected with other *Candida* species. *Candida krusei* candidemia was most commonly associated with prior use of antifungal agents (70.6%; $P < .001$), hematologic malignancy (52.9%; $P < .001$) or stem cell transplantation (17.7%; $P < .001$), neutropenia (45.1%; $P < .001$), and corticosteroid treatment (60.8%; $P < .001$). Patients with *C. krusei* candidemia had the highest crude 12-week mortality in this series (52.9%; $P < .001$). Fluconazole was the most commonly administered antimicrobial, followed by the echinocandins, and amphotericin B products were infrequently administered.

Conclusions. The epidemiology and choice of therapy for candidemia are rapidly changing. Additional study is warranted to differentiate host factors and differences in virulence among *Candida* species and to determine the best therapeutic regimen.

Candidemia is a major cause of morbidity and mortality in the health care setting. However, the incidence of candidemia is increasing with greater complexity of sur-

gical procedures, patient populations at higher risk of infection, and changes in patient demographic characteristics. Prolongation of survival among critically ill patients, especially in the intensive care unit setting, has led to increased use of invasive procedures, intravenous catheters, and intravenous hyperalimentation, all of which are risk factors for candidemia [1–3]. Recently, the introduction of additional antifungal agents has led to new strategies for empirical and prophylactic therapies. An increasing number of candidial infections are now caused by non-*Candida albicans* *Candida* species [4–10].

Candidemia remains associated with high crude and attributable mortality rates and with increased costs of

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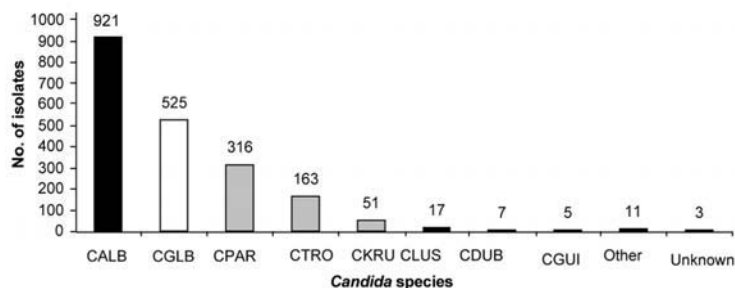


Figure 1. Distribution of isolated *Candida* species. CALB, *Candida albicans*; CDUB, *Candida dubliniensis*; CGLB, *Candida glabrata*; CGUI, *Candida guilliermondii*; CKRU, *Candida krusei*; CLUS, *Candida lusitanae*; CPAR, *Candida parapsilosis*; CTRO, *Candida tropicalis*.

care and duration of hospitalization. Attributable mortality has been reported to range from 5% to 71%, and crude mortality rates have been reported to be as high as 81% [11–23]. Inappropriate therapy or delays in initiation of therapy have also been linked to increased mortality [24, 25]. This study was performed to evaluate contemporary epidemiology and outcomes of candidemia in multiple North American centers.

METHODS

The patient population for this study was extracted from the Prospective Antifungal Therapy (PATH) Alliance database. The PATH Alliance is a comprehensive multicenter, prospective, observational registry that collects detailed clinical data on patients with invasive fungal infections (IFIs), with special emphasis on fungal epidemiology, diagnosis, treatment, and associated patient outcomes [26, 27].

This study is based on data for the 2019 patients (pediatric and adult) enrolled from 1 July 2004 through 5 March 2008 from 23 North American centers who received a diagnosis of proven candidemia. Detailed information with regard to candidemia episodes were analyzed, including underlying patient characteristics, the specific fungal pathogen and species, antifungal therapy, and survival.

A diagnosis of candidemia was made on the basis of ≥ 1 blood cultures growing *Candida* species and the presence of relevant clinical signs and symptoms, as enumerated in the guidelines of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group [28]. Only the first episode of candidemia was reported for patients with recurrent or subsequent episodes of infection. Patients whose cultures grew > 1 documented species of *Candida* were excluded from analysis. Some of these patients are described elsewhere [26].

Fisher's exact test or χ^2 test, as appropriate, was used for testing associations between categorical patient characteristics and *Candida* species. Analysis of variance was used for testing the difference in mean values across *Candida* species. Survival

distribution function was estimated using the Kaplan-Meier product-limit method; nonparametric (log-rank and Wilcoxon) tests were used to compare the survival functions among the different *Candida* species. Patients were considered to be lost to follow-up if they were discharged home or transferred to another institution prior to the 12-week assessment date and no additional information was available.

RESULTS

Among the 4010 patients with completed case reports of IFIs, 2019 patients (50.3%) with proven candidemia caused by a single species were identified by the PATH Alliance registry. The distribution of isolated *Candida* species is shown in figure 1. *C. albicans* was commonly identified (45.6%); however, collectively, non-*C. albicans* *Candida* species were more frequently isolated from blood cultures (54.4%). The majority of the other species identified included *Candida glabrata* (26.0%), *Candida parapsilosis* (15.7%), *Candida tropicalis* (8.1%), and *Candida krusei* (2.5%).

The mean age of patients was 53.5 years (range, 0–96.4 years), and 53.7% were male. Most of the patients were white (62.6%), followed by black (21.7%). Of note, 43.0% of the patients had received antifungal agents as prophylaxis or empirical therapy within 30 days prior to their diagnosis of candidemia. A comparison of patient characteristics across isolated *Candida* species is presented in table 1. Statistically significant differences were found in the distribution of *Candida* species with regard to age ($P < .001$), sex ($P = .002$), prior antifungal therapy ($P < .001$), presence of hematologic malignancy ($P < .001$), hematopoietic stem cell ($P < .001$) or solid organ transplantation ($P = .009$), neonatal intensive care unit stay ($P = .009$), surgery ($P = .04$), requirement of total parenteral nutrition ($P = .04$), mechanical ventilation ($P = .04$), use of central catheters (peripherally inserted, $P = .05$; tunneled, $P = .01$; nontunneled, $P = .03$), presence of neutropenia ($P < .001$), use of corticosteroids ($P < .001$) or other immunosuppressive agents ($P = .002$), and presence of concomitant bacterial infections ($P = .04$).

Table 1. Patient baseline characteristics, by isolated *Candida* species.

Characteristic	<i>Candida</i> species							P
	All (n = 2019)	<i>Candida albicans</i> (n = 921)	<i>Candida glabrata</i> (n = 525)	<i>Candida parapsilosis</i> (n = 316)	<i>Candida tropicalis</i> (n = 163)	<i>Candida krusei</i> (n = 51)	Other ^a (n = 43)	
Age, mean years (range)	53.5 (0–96.4)	51.9 (0–96.4)	58.7 (0.8–95.8)	50.1 (0–95.0)	53.8 (1.3–87.6)	49.7 (6.1–84.9)	50.9 (0–79.1)	<.001
Male sex	1084 (53.7)	502 (54.5)	251 (47.8)	173 (54.8)	105 (64.4)	24 (47.1)	29 (67.0)	.002
Ethnicity								
White	1264 (62.6)	571 (62.0)	342 (65.1)	193 (61.1)	93 (57.1)	32 (62.8)	33 (76.7)	.17
Black	439 (21.7)	200 (21.7)	115 (21.9)	69 (21.8)	41 (25.2)	6 (11.8)	8 (18.6)	.50
Hispanic	65 (3.2)	25 (2.7)	15 (2.9)	14 (4.4)	8 (4.9)	3 (5.9)	0 (0)	.26
Asian	24 (1.2)	10 (1.1)	5 (1.0)	4 (1.3)	3 (1.8)	1 (2.0)	1 (2.3)	.89
Other or unknown	227 (11.2)	115 (12.5)	48 (9.1)	36 (11.4)	18 (11.0)	9 (17.7)	1 (2.3)	.10
Prior antifungal therapy	869 (43.0)	358 (38.9)	272 (51.8)	119 (37.7)	68 (41.7)	36 (70.6)	16 (37.2)	<.001
Patient category ^b								
General medicine	1339 (66.3)	620 (67.3)	356 (67.8)	210 (66.5)	100 (61.4)	26 (51.0)	27 (62.8)	.14
Hematologic malignancy	197 (9.8)	54 (5.9)	51 (9.7)	23 (7.3)	34 (20.9)	27 (52.9)	8 (18.6)	<.001
Stem cell transplantation	58 (2.9)	13 (1.4)	19 (3.6)	9 (2.9)	5 (3.1)	9 (17.7)	3 (7.0)	<.001
HIV infection and/or AIDS	41 (2.0)	18 (2.0)	12 (2.3)	4 (1.3)	3 (1.8)	2 (3.9)	2 (4.7)	.61
Neonatal ICU stay	26 (1.3)	18 (2.0)	0 (0)	7 (2.2)	0 (0)	0 (0)	1 (2.3)	.009
Solid organ transplantation	166 (8.2)	65 (7.1)	64 (12.2)	20 (6.3)	10 (6.1)	3 (5.9)	4 (9.3)	.009
Solid tumor	351 (17.4)	167 (18.1)	94 (17.9)	45 (14.2)	26 (16.0)	9 (17.7)	10 (23.3)	.56
Surgical (nontransplantation)	662 (32.8)	317 (34.4)	159 (30.3)	117 (37.0)	48 (29.5)	9 (17.7)	12 (27.9)	.04
Organ function ^b								
Dialysis dependent	350 (17.3)	165 (17.9)	92 (17.5)	40 (12.7)	29 (17.8)	13 (25.5)	11 (25.6)	.09
Diabetes mellitus	705 (34.9)	314 (34.1)	198 (37.7)	107 (33.9)	60 (36.8)	11 (21.6)	15 (34.9)	.26
Total parenteral nutrition	751 (37.2)	349 (37.9)	197 (37.5)	131 (41.5)	50 (30.7)	11 (21.6)	13 (30.2)	.04
Mechanical ventilation	722 (35.8)	364 (39.5)	175 (33.3)	101 (32.0)	56 (34.4)	14 (27.5)	12 (27.9)	.04
Acute cardiac support	45 (2.2)	23 (2.5)	8 (1.5)	10 (3.2)	3 (1.8)	1 (2.0)	0 (0)	.57
Ventricular shunt	34 (1.7)	17 (1.9)	7 (1.3)	9 (2.9)	1 (0.6)	0 (0)	0 (0)	.32
Intravenous CC								
Peripherally inserted CC	714 (35.4)	317 (34.4)	175 (33.3)	136 (43.0)	57 (35.0)	18 (35.3)	11 (25.6)	.05
Tunneled CC	374 (18.5)	157 (17.0)	90 (17.1)	65 (20.6)	31 (19.0)	16 (31.4)	15 (34.9)	.01
Nontunneled CC	653 (32.3)	313 (34.0)	184 (35.0)	77 (24.4)	49 (30.1)	16 (31.4)	14 (32.6)	.03
Immune function ^b								
ANC <500 cells/mm ³	148 (7.3)	47 (5.1)	30 (5.7)	16 (5.1)	24 (14.7)	23 (45.1)	8 (18.6)	<.001
Corticosteroid therapy	828 (41.0)	369 (40.1)	225 (42.9)	106 (33.5)	71 (43.6)	31 (60.8)	26 (60.5)	<.001
Immunosuppressive therapy	208 (10.3)	78 (8.5)	77 (14.7)	25 (7.9)	15 (9.2)	5 (9.8)	8 (18.6)	.002
Concomitant infection ^b								
Cytomegalovirus	27 (1.3)	12 (1.3)	11 (2.1)	3 (1.0)	1 (0.6)	0 (0)	0 (0)	.47
Bacterial infection	1080 (53.5)	492 (53.4)	282 (53.7)	176 (55.7)	93 (57.1)	16 (31.4)	21 (48.8)	.04

NOTE. Data are no. (%) of patients, unless otherwise indicated. ANC, absolute neutrophil count; CC, central catheter; HIV, human immunodeficiency virus; ICU, intensive care unit.

^a Other species includes *Candida lusitanae* (17 cases), *Candida guilliermondii* (5), *Candida dubliniensis* (7), other (11), and unknown *Candida* species (3).

^b Patient category, organ function, immunologic risk factors, and concomitant infections were not mutually exclusive (patients could have >1 characteristic within a category).

The 316 patients with *C. parapsilosis* candidemia were least likely to have risk factors including nontunneled central catheter (24.4%), neutropenia (5.1%), or corticosteroid (33.5%) or other immunosuppressive therapies (7.9%); they were most likely to have had recent surgery (37.0%) or a peripherally inserted central venous catheter (43.0%). *C. krusei* candidemia (51 cases) was most commonly associated with younger age (mean age, 49.7 years), female sex (52.9%), prior use of antifungal agents (70.6%), hematologic malignancy (52.9%), stem cell transplantation (17.7%), neutropenia (45.1%), or corticosteroid therapy (60.8%), and patients with *C. krusei* candidemia were less likely to require total parenteral nutrition (21.6%) or mechanical ventilation (27.5%) or to have a concomitant bacterial infection (31.4%). The 525 patients with *C.*

glabrata candidemia were more likely to be older (mean age, 58.7 years) or to have undergone solid organ transplantation (12.2%). Patients with *C. albicans* candidemia were the least likely to have a hematologic malignancy (5.9%) and/or to have undergone stem cell transplantation (1.4%). Although rarely encountered, candidemia due to the rarest *Candida* species (e.g., *Candida dubliniensis* and *Candida lusitanae*) was more likely to occur in male patients (67.0%) or in patients who had tunneled central venous catheters (34.9%) or used immunosuppressive agents (18.6%).

Among the 2019 patients with candidemia, another 179 fungal infections due to *Candida* species were identified at sites other than blood, including the abdomen (95 cases [53.1%]), lungs (17 [9.5%]), skin and soft tissue (14 [7.8%]), eyes (9

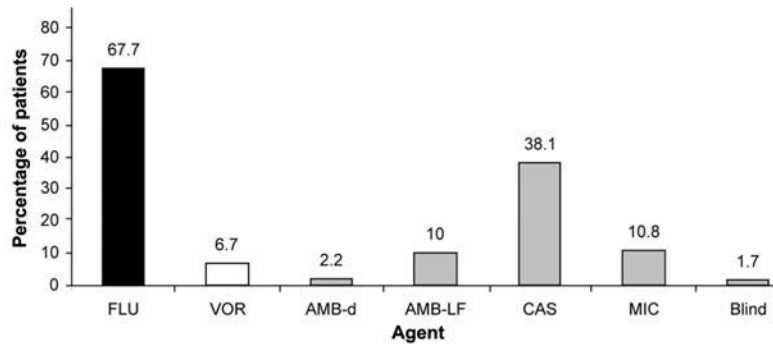


Figure 2. Administered antifungal agents; some patients received >1 agent. AMB-LF, any lipid formulation of amphotericin B; AMB-d, amphotericin B deoxycholate; CAS, caspofungin; FLU, fluconazole; MIC, micafungin; VOR, voriconazole.

[5.0%]), heart (7 [3.9%]), tracheobronchial tree (7 [3.9%]), skeleton (3 [1.7%]), central nervous system (2 [1.1%]), and other sites (25 [14.0%]). *C. albicans* was identified in 88 cases (49.2%); non-*C. albicans* *Candida* species collectively were more often isolated (91 cases [50.8%]). A small number of patients had a concomitant IFI other than *Candida* infection, including IFI due to *Aspergillus* species (11 patients), the Zygomycetes (1), endemic fungi (1), other molds (1), and other yeasts (5).

Administered antifungal agents are shown in figure 2. Fluconazole was most frequently used (67.7%), followed by caspofungin (38.1%). Micafungin was the third most frequently administered agent in this series (10.8%), followed by the lipid formulations of amphotericin B (10.0%) and voriconazole (6.7%). Amphotericin B deoxycholate was the agent that was least frequently administered (2.2%). A small minority of pa-

tients had received sequential or combination therapies (3.4%). Administered antifungal agents, stratified by *Candida* species, are shown in table 2. Fluconazole was most commonly used for cases of *C. albicans* candidemia (77.5%), and patients with *C. krusei* candidemia were the most likely to receive therapy with voriconazole (19.6%) or amphotericin B lipid formulations (27.4%). Echinocandins (caspofungin and micafungin) were used for the majority of patients with *C. glabrata* (66.3%) and *C. krusei* (74.5%) candidemia. A total of 138 patients (43.7%) with *C. parapsilosis* received an echinocandin.

Patient outcomes at 12 weeks and survival, stratified by *Candida* species, are reported in table 3 and figure 3, respectively. The overall, crude 12-week mortality rate was 35.2% (711 of 2019 patients died; 604 patients were lost to follow-up). *C. parapsilosis* candidemia was associated with the lowest 12-week mortality rate (23.7%). In contrast, patients with *C. krusei* can-

Table 2. Antifungal therapy administered, by different *Candida* species.

Antifungal agent	<i>Candida</i> species, no. (%) of treated cases						
	All (n = 2019)	<i>Candida albicans</i> (n = 921)	<i>Candida glabrata</i> (n = 525)	<i>Candida parapsilosis</i> (n = 316)	<i>Candida tropicalis</i> (n = 163)	<i>Candida krusei</i> (n = 51)	Other ^a (n = 43)
FLU	1366 (67.7)	714 (77.5)	273 (52.0)	233 (73.7)	98 (60.1)	16 (31.4)	32 (74.4)
VOR	136 (6.7)	45 (4.9)	44 (8.4)	21 (6.6)	12 (7.4)	10 (19.6)	4 (9.3)
AMB-D	44 (2.2)	23 (2.5)	6 (1.1)	9 (2.9)	2 (1.2)	2 (3.9)	2 (4.7)
ABCD	6 (0.3)	3 (0.3)	2 (0.4)	0 (0)	0 (0)	1 (2.0)	0 (0)
ABLC	86 (4.2)	33 (3.6)	12 (2.3)	25 (7.9)	10 (6.1)	4 (7.8)	2 (4.6)
L-AMB	110 (5.5)	38 (4.1)	24 (4.6)	27 (8.5)	7 (4.3)	9 (17.6)	5 (11.6)
LF-AMB	202 (10.0)	74 (8.0)	38 (7.2)	52 (16.4)	17 (10.4)	14 (27.4)	7 (16.3)
CAS	769 (38.1)	272 (29.5)	262 (49.9)	111 (35.1)	79 (48.5)	29 (56.9)	16 (37.2)
MIC	219 (10.9)	74 (8.0)	86 (16.4)	27 (8.5)	17 (10.4)	9 (17.7)	6 (14.0)
Blind ^b	34 (1.7)	18 (2.0)	7 (1.3)	4 (1.3)	2 (1.2)	3 (5.9)	0 (0)
Combination therapy ^c	68 (3.4)

NOTE. One patient received itraconazole or posaconazole, 3 patients received anidulafungin, and 6 patients received 5-fluorocytosine. ABCD, amphotericin (AMB) colloid dispersion; ABLC, AMB lipid complex; AMB-D, AMB deoxycholate; FLU, fluconazole; L-AMB, liposomal AMB; LF-AMB, any lipid formulation of AMB; CAS, caspofungin; MIC, micafungin; VOR, voriconazole.

^a Other species includes *Candida lusitanae* (17 cases), *Candida guilliermondii* (5), *Candida dubliniensis* (7), other (11), and unknown *Candida* species (3).

^b Blinded therapy as part of a clinical trial.

^c Some patients received ≥ 1 antifungal agents as combination and/or sequential therapy.

Table 3. Twelve-week outcome, by isolated *Candida* species.

Status at 12 weeks after diagnosis of IFI	<i>Candida</i> species, no. (%) of patients						
	All (n = 2019)	<i>Candida albicans</i> (n = 921)	<i>Candida glabrata</i> (n = 525)	<i>Candida parapsilosis</i> (n = 316)	<i>Candida tropicalis</i> (n = 163)	<i>Candida krusei</i> (n = 51)	Other ^a (n = 43)
Alive	704 (34.9)	306 (33.2)	189 (36.0)	124 (39.2)	50 (30.7)	17 (33.3)	18 (41.9)
Dead	711 (35.2)	328 (35.6)	200 (38.1)	75 (23.7)	67 (41.1)	27 (52.9)	14 (32.6)
Unknown	604 (29.9)	287 (31.2)	136 (25.9)	117 (37.0)	46 (28.2)	7 (13.7)	11 (25.6)

NOTE. $P < .001$, by log-rank test.

^a Other species included *Candida lusitanae* (17 cases), *Candida guilliermondii* (5), *C. dubliniensis* (7), other (11), and unknown *Candida* species (3).

didemia had the highest mortality rate (52.9%) in this cohort. A statistically significant difference in the 12-week survival distributions by *Candida* species ($P < .001$) was found (figure 3). Survival patterns among patients with candidemia due to *C. albicans*, *C. glabrata*, *C. tropicalis*, and other *Candida* species were similar. A statistically significant difference in the 12-week survival distributions ($P < .001$) was found based on age (83.2% for 0 to <19 years of age, 68.7% for 19–65 years of age, and 52.7% for >65 years of age) (figure 4). When analyzed by *Candida* species and age group, a similar pattern was seen with *C. albicans* ($P < .001$), *C. glabrata* ($P < .002$), and *C. parapsilosis* ($P < .007$). No statistically significant differences were observed with *C. tropicalis*, *C. krusei*, or other *Candida* species. No statistically significant difference in the 12-week survival distributions was found when analyzed by ethnicity (data not shown).

DISCUSSION

A cohort of 2019 patients with candidemia was identified and analyzed from the PATH Alliance registry, a prospective data-

base of IFIs at major North American medical centers. To our knowledge, this is the largest cohort of patients with candidemia, with contemporary patients enrolled from July 2004 through March 2008. Other large series of patients with candidemia were from earlier periods, enrolled from 1991 through 2000 (1137 episodes of candidemia) [29] and from February 1995 through November 1997 (1447 adults and 144 children with candidemia) [8]. We observed a predominance of non-*C. albicans* *Candida* species (54.4%); *C. albicans* was the most frequently isolated species (45.6%). We report an overall, 12-week crude mortality rate of 35.2% among patients who experienced a single episode of candidemia, with the lowest mortality observed among patients with *C. parapsilosis* candidemia and the highest among patients with *C. krusei* candidemia.

Candidemia has been identified among the most common etiologic agents of bloodstream infections. It ranked seventh in a nationwide survey of 17 hospitals in Switzerland [29] and fourth in the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) surveillance study of bloodstream infections in hospitalized patients in the United States

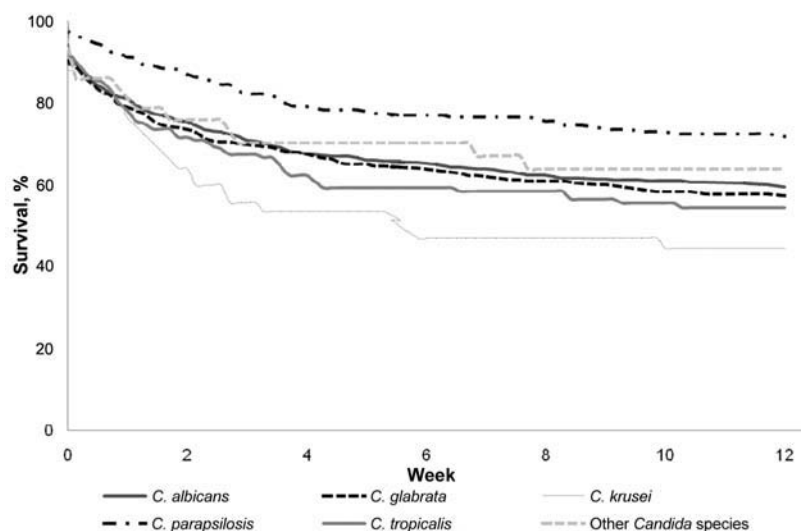


Figure 3. Survival among patients with candidemia at 12 weeks, by *Candida* species (*Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, and *Candida tropicalis*).

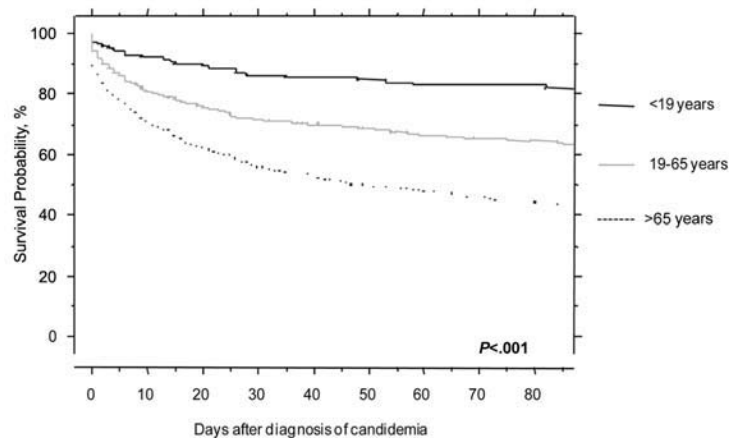


Figure 4. Survival among patients with candidemia at 12 weeks, by age group

[30]. *C. albicans* has traditionally been the predominant *Candida* species isolated, followed by *C. glabrata* and other non-*C. albicans* *Candida* species, in both pediatric and adult patient populations [8, 29, 30]. In a worldwide surveillance program (1997–2003) that included 134,715 consecutive clinical isolates of *Candida* species from 127 medical centers in 39 countries, a trend toward a decrease in *C. albicans* and an increase in *C. tropicalis* and *C. parapsilosis* was noted [31]. In addition, species distribution differences have been reported throughout the world. For example, *C. albicans* and *C. glabrata* were most frequently identified in series from Denmark and the United States, although South America had lower rates of these species [31].

In this study population from the PATH Alliance, non-*C. albicans* *Candida* species were more frequently isolated than was *C. albicans* (54.4% vs. 45.6%). Patients with *C. glabrata* and *C. krusei* candidemia were the most likely to have received prior antifungal therapy. This likely reflects, in part, selective pressure because of the extensive use of prophylactic fluconazole in susceptible hosts [32, 33]. In addition, severe immunosuppression or illness, prematurity, exposure to broad-spectrum antibiotics, and older age may contribute to the increased incidence of candidemia caused by non-*C. albicans* *Candida* species, especially *C. glabrata*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis* [34–41]. We observed an association between neutropenia and the use of corticosteroids and *C. krusei* candidemia, consistent with the underlying medical conditions of these patients, including hematologic malignancy and stem cell transplantation, and the associated prior use of azole prophylaxis. Patients with *C. krusei* candidemia were younger and did not generally have such additional risk factors as parenteral nutrition, mechanical ventilation, and concomitant bacterial infections. Older age and receipt of a solid organ transplant were associated with *C. glabrata* candidemia. Our observations

suggest that the changing patient population and practices involved in their care may contribute to the continual shift in the epidemiology of *Candida* species.

In the present study, the azole antifungals were the most frequently administered antifungal agents, followed by the echinocandins. Combination therapy remains an uncommon practice in the treatment of candidemia. Overall, amphotericin B products were infrequently administered, especially amphotericin B deoxycholate, which was used for <3% of patients. The relatively recent introduction of echinocandins and azoles will necessitate re-evaluation of clinical outcomes of therapy for candidemia over time. The differences observed in the use of antifungal agents based on the different *Candida* species may, in part, be explained by the variations in their susceptibility profiles (when available), empirical therapy based on existing treatment guidelines [10], or differences in clinical practice, including prophylactic programs, among the participating centers. As outlined in the recently revised guidelines for the treatment of candidemia by the Infectious Diseases Society of America, treatment should be adjusted on the basis of the *Candida* species isolated (42).

Retrospective cohort studies involving patients with candidemia and varying underlying diseases have revealed worldwide crude and attributable mortality rates of 30%–81% and 5%–71%, respectively [11–22]. In our series, patients with candidemia had a crude 12-week mortality rate of 35.2%. Survival appears to be improved, compared with that in many older studies. The identification of candidemia as one of the leading causes of bloodstream infections [30] and greater knowledge of major risk factors for candidemia [21] have likely led to higher clinical suspicion, prompt initiation of diagnostic testing, and pre-emptive or empirical treatment with new, effective, and well-tolerated antifungal agents. In this series, the use of nonculture diagnostic methods was rarely a factor in the ini-

tiation of antifungal therapy (<1%). Thus, improved outcomes could not be attributed to these diagnostic tools.

The highest and lowest crude mortality rates reported in the SCOPE surveillance study [30] were for *C. krusei* and *C. parapsilosis* candidemia. Similarly, candidemia due to *C. krusei* was associated with the highest mortality rate observed in this series (52.9%). This can be explained, in part, by underlying immune deficits in the patient populations most frequently affected by these species, including patients with hematologic malignancies and stem cell transplant recipients. Our findings suggest that patients with *C. parapsilosis* candidemia have the lowest mortality rate (23.7%); this finding is consistent with the results of prior studies [20, 30, 43]. These patients were less likely to be neutropenic or to be receiving corticosteroids and other immunosuppressive agents; this is consistent with the mechanism by which *C. parapsilosis* causes infection, in association with contaminated infusates and catheters. As was reported in a separate analysis [44], we observed similar mortality rates for *C. albicans* and *C. glabrata* candidemia in this study. Our findings, based on a large number of patients, strongly suggest that there may not be significant differences in survival associated with infection due to the 2 most common *Candida* species. Additional prospective or case-control studies are needed to delineate differences between other specific *Candida* species.

Limitations of the present study include differences in clinical practices across different centers, limited follow-up data, the inability to clearly distinguish between prophylactic and empirical therapy or sequential and concomitant antifungal therapy, and the collection of data from only institutions in North America. Despite these limitations, the data collected by the PATH Alliance registry include a very large number of patients with IFIs with a broad spectrum of underlying conditions. This database will likely prove to be a significant asset in the understanding of IFIs, including candidemia [45]. Differences in the outcomes and presentations of IFIs will be addressed by the PATH Alliance with large cohort studies and case-control studies to provide more information on optimal approaches to candidemia and other IFIs.

PROSPECTIVE ANTIFUNGAL THERAPY (PATH) ALLIANCE

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References

1. Pelz RK, Hendrix CW, Swoboda SM, et al. Double-blind placebo-controlled trial of fluconazole to prevent candidal infections in critically ill surgical patients. *Ann Surg* **2001**;233:542–8.
2. Peres-Bota D, Rodriguez-Villalobos H, Dimopoulos G, Melot C, Vincent JL. Potential risk factors for infection with *Candida* spp. in critically ill patients. *Clin Microbiol Infect* **2004**;10:550–5.
3. Wenzel RP. Nosocomial candidemia: risk factors and attributable mortality. *Clin Infect Dis* **1995**;20:1531–4.
4. Marr KA. Invasive *Candida* infections: the changing epidemiology. *Oncology (Williston Park)* **2004**;18(Suppl 13):9–14.
5. Nucci M, Marr KA. Emerging fungal diseases. *Clin Infect Dis* **2005**;41:521–6.
6. Trick WE, Fridkin SK, Edwards JR, Hajjeh RA, Gaynes RP. Secular trend of hospital-acquired candidemia among intensive care unit patients in the United States during 1989–1999. *Clin Infect Dis* **2002**;35:627–30.
7. Fridkin SK. The changing face of fungal infections in health care settings. *Clin Infect Dis* **2005**;41:1455–60.
8. Pappas PG, Rex JH, Lee J, et al. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. *Clin Infect Dis* **2003**;37:634–43.
9. Blumberg HM, Jarvis WR, Soucie JM, et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. *The National Epidemiology of Mycosis Survey*. *Clin Infect Dis* **2001**;33:177–86.
10. Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. *Clin Infect Dis* **2004**;38:161–89.
11. Morgan J, Meltzer MI, Plikaytis BD, et al. Excess mortality, hospital stay, and cost due to candidemia: a case-control study using data from population-based candidemia surveillance. *Infect Control Hosp Epidemiol* **2005**;26:540–7.
12. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Hospital-acquired candidemia: the attributable mortality and excess length of stay. *Arch Intern Med* **1988**;148:2642–5.
13. Gudlaugsson O, Gillespie S, Lee K, et al. Attributable mortality of nosocomial candidemia, revisited. *Clin Infect Dis* **2003**;37:1172–7.
14. Chen S, Slavin M, Nguyen Q, et al. Active surveillance for candidemia, Australia. *Emerg Infect Dis* **2006**;12:1508–16.
15. Poikonen E, Lytikainen O, Anttila VJ, Ruutu P. Candidemia in Finland, 1995–1999. *Emerg Infect Dis* **2003**;9:985–90.
16. Pagano L, Caira M, Candoni A, et al. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica* **2006**;91:1068–75.
17. Anaissie EJ, Rex JH, Uzun O, Vartivarian S. Predictors of adverse outcome in cancer patients with candidemia. *Am J Med* **1998**;104:238–45.
18. Nieto-Rodriguez JA, Kusne S, Manez R, et al. Factors associated with the development of candidemia and candidemia-related death among liver transplant recipients. *Ann Surg* **1996**;223:70–6.
19. Nolla-Salas J, Sitges-Serra A, Leon-Gil C, et al. Candidemia in non-neutropenic critically ill patients: analysis of prognostic factors and assessment of systemic antifungal therapy. Study Group of Fungal Infection in the ICU. *Intensive Care Med* **1997**;23:23–30.
20. Viscoli C, Girmenia C, Marinus A, et al. Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). *Clin Infect Dis* **1999**;28:1071–9.
21. Ostrosky-Zeichner L. New approaches to the risk of *Candida* in the intensive care unit. *Curr Opin Infect Dis* **2003**;16:533–7.
22. Colombo AL, Nucci M, Park BJ, et al. Epidemiology of candidemia in Brazil: a nationwide sentinel surveillance of candidemia in eleven medical centers. *J Clin Microbiol* **2006**;44:2816–23.
23. Zaoutis TE, Argon J, Chu J, Berlin JA, Walsh TJ, Feudtner C. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. *Clin Infect Dis* **2005**;41:1232–9.
24. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis* **2006**;43:25–31.
25. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. *Antimicrob Agents Chemother* **2005**;49:3640–5.
26. Horn D, Neofytos D, Fishman J, et al. Use of the PATH Alliance database to measure adherence to IDSA guidelines for the therapy of candidemia. *Eur J Clin Microbiol Infect Dis* **2007**;26:907–14.
27. Horn DL, Fishman JA, Steinbach WJ, et al. Presentation of the PATH Alliance(R) registry for prospective data collection and analysis of the epidemiology, therapy, and outcomes of invasive fungal infections. *Diagn Microbiol Infect Dis* **2007**;59:407–14.
28. Ascoglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* **2002**;34:7–14.
29. Marchetti O, Bille J, Fluckiger U, et al. Epidemiology of candidemia in Swiss tertiary care hospitals: secular trends, 1991–2000. *Clin Infect Dis* **2004**;38:311–20.
30. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* **2004**;39:309–17.
31. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. *Clin Microbiol Rev* **2007**;20:133–63.
32. Wingard JR, Merz WG, Rinaldi MG, Johnson TR, Karp JE, Saral R. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. *N Engl J Med* **1991**;325:1274–7.
33. Wingard JR, Merz WG, Rinaldi MG, Miller CB, Karp JE, Saral R. Association of *Torulopsis glabrata* infections with fluconazole prophylaxis in neutropenic bone marrow transplant patients. *Antimicrob Agents Chemother* **1993**;37:1847–9.
34. Yamamura DL, Rotstein C, Nicolle LE, Ioannou S. Candidemia at selected Canadian sites: results from the Fungal Disease Registry, 1992–1994. *Fungal Disease Registry of the Canadian Infectious Disease Society*. *Cmaj* **1999**;160:493–9.
35. Nguyen MH, Peacock JE Jr, Morris AJ, et al. The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. *Am J Med* **1996**;100:617–23.
36. Abi-Said D, Anaissie E, Uzun O, Raad I, Pinzcowski H, Vartivarian S. The epidemiology of hematogenous candidiasis caused by different *Candida* species. *Clin Infect Dis* **1997**;24:1122–8.
37. Kossoff EH, Buescher ES, Karlowicz MG. Candidemia in a neonatal intensive care unit: trends during fifteen years and clinical features of 111 cases. *Pediatr Infect Dis J* **1998**;17:504–8.
38. Bassetti M, Righi E, Tumbarello M, Di Biagio A, Rosso R, Viscoli C. *Candida* infections in the intensive care unit: epidemiology, risk factors and therapeutic strategies. *Expert Rev Anti Infect Ther* **2006**;4:875–85.
39. Dotis J, Evdoridou J, Kremenopoulos G, Rollides E. Survey of neonatal candidiasis in Greece. *Eur J Clin Microbiol Infect Dis* **2005**;24:749–52.
40. Rodriguez D, Almirante B, Park BJ, et al. Candidemia in neonatal intensive care units: Barcelona, Spain. *Pediatr Infect Dis J* **2006**;25:224–9.
41. Vigouroux S, Morin O, Moreau P, Harousseau JL, Milpied N. Candidemia in patients with hematologic malignancies: analysis of 7 years' experience in a single center. *Haematologica* **2006**;91:717–8.
42. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* **2009**;48:503–35.
43. Kullberg BJ, Sobel JD, Ruhnke M, et al. Voriconazole versus a regi-

- men of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. *Lancet* **2005**;366:1435–42.
44. Klevay MJ, Horn DL, Neofytos D, Pfaller MA, Diekema DJ; for the PATH Alliance. Initial treatment and outcome of *Candida glabrata* versus *Candida albicans* bloodstream infection. *Diagn Microbiol Infect Dis* **2009** (Epub ahead of print).
45. Horn D, Neofytos D. Contemporary patterns in the use of antifungal agents in the treatment of invasive fungal infections: perspectives from registries and databases. *Curr Fungal Infect Rep* **2007**;1:72–78.