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Prevalence and Antifungal Susceptibility of 442 *Candida* Isolates from Blood and Other Normally Sterile Sites: Results of a 2-Year (1996 to 1998) Multicenter Surveillance Study in Quebec, Canada

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During a 2-year surveillance program (1996 to 1998) in Quebec, Canada, 442 strains of *Candida* species were isolated from 415 patients in 51 hospitals. The distribution of species was as follows: *Candida albicans,* 54%; *C. glabrata,* 15%; *C. parapsilosis,* 12%; *C. tropicalis,* 9%; *C. lusitaniae,* 3%; *C. krusei,* 3%; and *Candida* spp., 3%. These data, compared to those of a 1985 survey, indicate variations in species distribution, with the proportions of *C. glabrata* and *C. parapsilosis* increasing by 9 and 4%, respectively, and those of *C. albicans* and *C. tropicalis* decreasing by 10 and 7%, respectively. However, these differences are statistically significant for *C. glabrata* and *C. tropicalis* only. MICs of amphotericin B were ≥4 μg/ml for 3% of isolates, all of which were non-*C. albicans* species. Three percent of *C. albicans* isolates were resistant to flucytosine (≥32 μg/ml). Resistance to itraconazole (≥1 μg/ml) and fluconazole (≥64 μg/ml) was observed, respectively, in 1 and 1% of *C. albicans*, 14 and 9% of *C. glabrata*, 5 and 0% of *C. tropicalis,* and 0% of *C. parapsilosis* and *C. lusitaniae* isolates. Clinical data were obtained for 343 patients. The overall crude mortality rate was 38%, reflecting the multiple serious underlying illnesses found in these patients. Bloodstream infections were documented for 249 patients (73%). Overall, systemic triazoles had been administered to 10% of patients before the onset of candidiasis. The frequency of isolation of non-*C. albicans* species was significantly higher in this group of patients. Overall, only two *C. albicans* isolates were found to be resistant to fluconazole. These were obtained from an AIDS patient and a leukemia patient, both of whom had a history of previous exposure to fluconazole. At present, it appears that resistance to fluconazole in Quebec is rare and is restricted to patients with prior prolonged azole treatment.

The incidence of nosocomial fungal infections has increased substantially over the past 2 decades, and this increase is likely associated with the growing population of patients undergoing chemotherapy, transplant surgery, and intensive care support (7, 8, 28). Species of the genus *Candida* are the agents most frequently implicated in invasive fungal infections, and they now rank as the fourth most common cause of nosocomial bloodstream infections in the United States (7). A recent study in two United States cities reported an annual incidence for candidemia of 8 per 100,000 population, a rate higher than that for various invasive bacterial infections, such as invasive meningococcal and invasive group B streptococcal diseases (8). Several surveillance programs have produced data documenting these increases and have documented trends in species distribution and antifungal susceptibility (2, 8, 12, 14–16, 23, 29). Some variations have been shown to occur among institutions, localities, or countries. These may be due to differences in antifungal prescription and infection control practices. Pfaller et al. have reported differences in the distribution of species and resistance to triazoles among various regions of the United States (16). In view of the increasing problem posed by *Candida* nosocomial infections and the added concern of the emergence of antifungal resistance, a prospective surveillance program for yeasts isolated from normally sterile sites was instituted in the province of Quebec, Canada, for the years 1996 to 1998. The main objectives were to obtain data regarding the spectrum of *Candida* species involved, along with their antifungal susceptibility, and to study the demographic and clinical features of *Candida* nosocomial infections in the province of Quebec.

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MATERIALS AND METHODS

Data collection and clinical isolates. The data were collected in the course of a 2-year surveillance program from October 1996 to October 1998. Strains (one strain per species per patient) of *Candida* isolated from blood or other normally sterile sites in hospital laboratories throughout the province of Quebec were sent to the provincial reference laboratory for further analysis. Demographic and clinical data were recorded on a standardized form and included age, sex, site of isolation, infectious diagnosis, underlying conditions, predisposing factors, history of exposure to antifungal agents before and after detection of the isolates, central venous catheter withdrawal and culturing, and clinical outcome. In order to explore issues regarding flucytosine and azole susceptibility testing methods, a group of 43 *Candida albicans* isolates from a previous surveillance study dating back to 1985 (26) was tested with our current method.

Organism identification. Organisms were identified by germ tube analysis and morphology evaluation on cornmeal-Tween 80 agar or, when necessary, by carbohydrate assimilation tests with API 20C AUX strips (bioMérieux Vitek, Inc., Hazelwood, Mo.) supplemented with a urease test.

Susceptibility testing. Testing was performed by a broth microdilution method following the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS) (9). The culture media used were RPMI 1640 for flucytosine and the azoles and M3 broth supplemented with 2% glucose for amphotericin B. Inhibitory concentrations were recorded spectrophotometrically

TABLE 1. Clinical data for 343 patients with nosocomial candidiasis

Characteristic	No. (%) of patients
Sites of isolation	
Blood	249 (73)
Sterile body fluids	55 (16)
Catheter	17 (5)
Tissue	10 (3)
Underlying conditions	
Malignant disease	96 (28)
Diabetes	24 (7)
Transplantation	20 (6)
Renal insufficiency	20 (6)
Burn	10 (3)
Trauma	6 (2)
Human immunodeficiency virus infection	6 (2)
Prematurity	5 (2)
Predisposing factors	
Antibacterial therapy	232 (68)
Central venous catheter	207 (60)
Stay in intensive care unit	155 (45)
Major surgery	139 (41)
Parenteral nutrition	138 (40)
Steroid therapy	67 (20)
Neutropenia	43 (13)
Central venous catheter	
Present	207 (60)
Withdrawn	175 (85)
Cultured (no. positive for yeast)	85 (49)
Mortality	130 (38)
Antifungal treatments (prediagnosis)	
Fluconazole	32 (9)
Itraconazole	4 (1)
Amphotericin B	9 (3)
Antifungal treatments (postdiagnosis)	
Fluconazole	210 (61)
Itraconazole	7 (2)
Amphotericin B	152 (44)

after both 24 and 48 h of incubation in air at 35°C. The plates were agitated for 3 min at 900 rpm with a shaker (model EAS 2/4; SLT Lab Instruments, Grödig, Austria), and the optical density (OD) of the growth in each well was determined with the use of an automatic plate reader set at 495 nm (Pasteur Diagnostic LP400; Adil Instruments, Strasbourg, France). The data were transferred to a spreadsheet, where the OD of the medium control well was subtracted from the ODs of all other wells and inhibitory concentrations were computed mathematically. The MIC of amphotericin B was determined as the lowest drug concentration with an OD corresponding to a ≥90% decrease in turbidity compared to that of the growth control, and the MIC of the other drugs corresponded to a 50% decrease in turbidity (10, 17, 19). Quality control was performed by testing *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 with each batch of clinical isolates (9). *C. lusitaniae* 5W31, kindly provided by John Rex (University of Texas Health Science Center), was also tested repeatedly as a reference isolate for amphotericin B resistance (21).

Interpretive guidelines. The interpretive breakpoints for flucytosine, itraconazole, and fluconazole were those of the NCCLS (9). Although at present no guidelines are available for amphotericin B, we chose to use the modal MIC obtained with *C. lusitaniae* 5W31 as a reference for resistance (4 μg/ml at 48 h).

Statistical analyses. Statistical analyses were performed with Epi Info 6.04btoc software (Centers for Disease Control and Prevention and World Health Organization). Relationships between proportions were analyzed by chi-square tests. A two-sided *P* value of less than 0.05 was used to determine statistical significance.

RESULTS

Patient population and clinical data. During this 2-year study, a total of 415 cases of nosocomial candidiasis were reported by 51 hospital laboratories. These were diagnosed in 223 male and 191 female patients ranging in age from 1 day to 95 years, with a mean of 51 years and a median of 57 years. Clinical data questionnaires were completed for 343 patients, and the data are shown in Table 1. In these patients, the overall mortality rate was 38%; the mortality rate increased to 43% for patients with candidemia and 52% for those in intensive care units. The lowest and highest mortality rates were observed with *C. parapsilosis* (30%) and *C. glabrata* (49%), respectively. A central venous catheter was present in 207 patients. In the 27 patients whose catheters were not removed, the mortality rate was 78%; the mortality rate was 34% in those whose catheters were removed. Triazoles had been administered to 10% of patients before the onset of candidiasis. Forty-nine patients (14%) had not been treated with any antifungal agent.

Etiology. A total of 442 *Candida* isolates were received for analysis, and the overall distribution of species is shown in Table 2. A comparable distribution rate was observed for candidemia patients, with *C. albicans* being recovered from 55% of patients, followed by *C. glabrata* (17%), *C. parapsilosis* (11%), *C. tropicalis* (7%), *C. lusitaniae* (3%), and *C. krusei* (3%). The *Candida* species recovered from the 34 patients treated with systemic azole agents before the onset of candidiasis were predominantly non-*C. albicans* and included 13 isolates of *C. albicans,* 8 of *C. glabrata*, 4 of *C. krusei,* 3 each of *C. tropicalis* and *C. parapsilosis*, and 1 each of *C. lusitaniae, C. guilliermondii,* and *C. lipolytica*.

Susceptibility to amphotericin B. During the course of this study, the modal MICs for *C. lusitaniae* 5W31 after 24 and 48 h of incubation were 2 and 4 μg/ml, respectively, and these values were chosen as interpretative breakpoints for resistance to amphotericin B. For none of the clinical isolates in our study were amphotericin B MICs ≥2 μg/ml after 24 h of incubation (Table 3). However, at 48 h, the MICs were ≥4 μg/ml for 14 isolates, including 7 *C. krusei*, 5 *C. glabrata,* and 2 *C. lusitaniae* isolates.

Susceptibility to flucytosine. Resistance to flucytosine could not be detected in any of our *C. albicans* isolates at 24 h when the 48-h NCCLS breakpoint of ≥32 μg/ml was used. Only 3% of these isolates were found resistant to flucytosine at 48 h (Table 3). Among the 43 *C. albicans* isolates from our 1985 survey, 11 were originally found resistant to flucytosine (≥100 μg/ml) by a broth macrodilution method using yeast nitrogen base with glucose. None of these isolates was found resistant within 48 h when the NCCLS M27-A broth microdilution method was used.

TABLE 2. Species distribution of 442 *Candida* strains isolated from normally sterile sites in the course of a 2-year surveillance program from 1996 to 1998

Species	No. (%) of isolates
C. albicans	240 (54.3)
C. glabrata	67 (15.2)
C. parapsilosis	53 (12.2)
C. tropicalis	41 (9.3)
C. lusitaniae	15 (3.4)
C. krusei	15 (3.4)
Other[a]	11 (2.2)

[a] Including three isolates of *C. guilliermondii*, two each of *C. famata* and *C. utilis*, and one each of *C. rugosa*, *C. lipolytica*, *C. pelliculosa*, and *Candida* sp.

TABLE 3. In vitro susceptibilities of *Candida* species to four antifungal agents after 24 and 48 h of incubation

Species (no. of isolates)	Antifungal agent	MIC (μg/ml) at the indicated time[a]: Range		50%		90%		% Resistant at[b]:	
		24 h	48 h	24 h	48 h	24 h	48 h	24 h	48 h
C. albicans (240)	Amphotericin B	0.6–1	0.25–2	0.12	0.5	0.25	1	0	0
	Flucytosine	≤0.06–4	≤0.06–>64	≤0.06	0.12	0.25	1	0	3
	Itraconazole	≤0.008–>8	≤0.008–>8	0.016	0.03	0.03	>8	1	21
	Fluconazole	≤0.25–>256	≤0.25–>256	≤0.25	0.5	≤0.25	128	1	13
C. glabrata (67)	Amphotericin B	0.12–1	0.5–4	0.25	1	1	4	0	7
	Flucytosine	≤0.06–4	≤0.06–4	≤0.06	≤0.06	≤0.06	0.12	0	0
	Itraconazole	0.003–4	0.06–>8	0.25	1	1	4	13	58
	Fluconazole	1–>256	2–>256	4	8	64	64	9	13
C. parapsilosis (53)	Amphotericin B	0.03–0.5	0.06–2	0.12	0.5	0.25	1	0	0
	Flucytosine	≤0.06–0.12	≤0.06–1	≤0.06	0.12	≤0.06	0.25	0	0
	Itraconazole	≤0.008–0.25	0.016–0.5	0.03	25	0.12	0.25	0	0
	Fluconazole	≤0.25–1	≤0.25–4	0.5	1	1	2	0	0
C. tropicalis (41)	Amphotericin B	0.06–1	0.25–2	0.25	1	0.5	1	0	0
	Flucytosine	≤0.06–>64	≤0.06–>64	≤0.06	0.25	0.12	64	5	10
	Itraconazole	≤0.008–4	≤0.016–>8	0.06	0.25	0.5	>8	5	32
	Fluconazole	≤0.25–16	≤0.25–>256	0.5	1	8	>256	0	27
C. lusitaniae (15)	Amphotericin B	0.12–1	0.5–4	0.5	1	1	4	0	13
	Flucytosine	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0	0
	Itraconazole	0.016–0.12	0.03–0.5	0.03	0.12	0.12	0.25	0	0
	Fluconazole	≤0.25–32	≤0.25–32	0.5	0.5	2	7	0	0
C. krusei (15)	Amphotericin B	0.5–1	0.5–8	0.5	2	1	4	0	47
	Flucytosine	2–8	4–32	8	16	8	16	0	7
	Itraconazole	0.12–1	0.25–2	0.25	0.5	0.5	1	7	47
	Fluconazole	8–64	16–128	16	64	64	128	13	53[c]

[a] Inhibitory concentrations were determined spectrophotometrically by a microdilution method: ≥90% decrease in turbidity for amphotericin B and ≥50% decrease in turbidity for flucytosine, itraconazole, and fluconazole. 50% and 90%, MICs at which 50 and 90% of isolates were inhibited, respectively.

[b] Defined as follows: amphotericin B resistance, ≥2 μg/ml at 24 h and ≥4 μg/ml at 48 h; flucytosine resistance, ≥32 μg/ml; itraconazole resistance, ≥1.0 μg/ml; and fluconazole resistance, ≥ 64 μg/ml.

[c] Isolates of *C. krusei* were considered resistant to fluconazole irrespective of the MIC.

Susceptibility to triazoles. Two and 13% of all isolates were resistant to fluconazole at 24 and 48 h, respectively, while 3 and 26% were resistant to itraconazole. Eighty-nine percent of isolates (eight of nine) resistant to fluconazole at 24 h were cross-resistant to itraconazole. Overall, 21 patients had *C. albicans* isolates resistant to fluconazole at 48 h (≥64 μg/ml). Nine of these patients were treated with fluconazole only: seven were cured, one improved, and one had an undetermined clinical outcome. Fungemia diagnosed after fluconazole treatment was observed in 4 out of these 21 patients. *C. albicans* isolates from two of these patients, one with AIDS and the other with leukemia, were the only ones found to be resistant at both 24 and 48 h. These two isolates were also resistant to itraconazole. Both patients were eventually treated with amphotericin B. None of eight *C. tropicalis* isolates resistant to fluconazole at 48 h was resistant at 24 h, and none was from patients previously exposed to azoles.

DISCUSSION

A total of 415 cases of nosocomial candidiasis were reported during the course of this surveillance program in Quebec. Although *C. albicans* remains the most common species recovered, at 54% of isolates, the frequency of non-*C. albicans* species has increased over the last decade. A similar Quebec surveillance program conducted in 1985 revealed the following distribution of species in 84 patients with *Candida* nosocomial infections: *C. albicans,* 64%; *C. tropicalis*, 17%; *C. parapsilosis,* 8%; *C. glabrata,* 6%; *C. krusei,* 2%; *C. lusitaniae,* 1%; and *Candida* sp., 1% (26). In comparison, the data from the present study indicated 10% ($P = 0.09$) and 7% ($P = 0.04$) decreases in the proportions of *C. albicans* and *C. tropicalis,* respectively, while those of *C. glabrata* and *C. parapsilosis* increased by 9% ($P = 0.02$) and 4% ($P = 0.33$), respectively. Similar shifts in distribution have been observed by others, especially for *C. glabrata* (8, 12, 15). Despite the more widespread use of fluconazole, the proportion of *C. krusei* has remained virtually unchanged at 2% and is similar to that reported in other studies (2, 8, 14, 15, 23). However, we did notice a higher frequency of non-*C. albicans* isolates among patients who had been treated with azoles before the onset of candidiasis. The overall proportion of 46% non-*C. albicans* species rose to 62% among the 34 patients with prior exposure to fluconazole or itraconazole ($P = 0.04$). Thirty-six percent of *C. krusei* and 15% of *C. glabrata* strains were isolated from these 34 patients, compared to 10% of *C. lusitaniae,* 9% of *C. tropicalis*, 8% of *C. parapsilosis,* and 7% of *C. albicans* strains. It is unclear whether these findings are due to selective pressure related to fluconazole exposure, given that the overall

proportion of *C. krusei* isolates is similar to rates reported in the prefluconazole era. The overall distribution of *Candida* species involved in nosocomial infections in Quebec appears to be similar to that recently reported in the United States by Pfaller et al. (14).

The predisposing factors and underlying diseases observed in this study are comparable to those observed by others (8, 28). Among these, central venous lines are an important risk factor for candidemia, and failure to perform catheter exchange was strongly associated with the persistence of infection (20). In our study, the mortality rate for patients whose catheters were not removed was much higher than that for patients in whom catheters were replaced (78 versus 34%). However, additional cofactors, such as the severity of underlying diseases, also may be important in explaining these differences in mortality rates.

There is a consensus that candidemia, regardless of its source or duration, should be treated with systemic antifungal drugs (3). Studies have reported rates of untreated patients as high as 35% (2, 13). In our study, 31 patients (12%) were reported as not having been specifically treated for candidemia. The reasons for this were not always clear, although terminal disease and postmortem diagnosis were often evoked. Not surprisingly, a higher mortality rate (65%) was observed in candidemia patients not receiving antifungal therapy than in treated patients (39%).

Resistance of *Candida* spp. to amphotericin B is considered uncommon (28) but has been documented, especially for *C. lusitaniae* (6). However, it must be kept in mind that important methodology issues still need to be resolved, as NCCLS method M27-A may not be efficient in detecting amphotericin B resistance (9, 21). None of the *Candida* isolates in this study was found resistant to amphotericin B, unlike *C. lusitaniae* isolate 5W31, after 24 h of incubation. However, after 48 h, MICs for 14 isolates were $\geq$4 μg/ml. These were all non-*C. albicans* species. MICs at which 90% of isolates were inhibited (4 μg/ml) were high for *C. krusei*, *C. glabrata,* and *C. lusitaniae,* species previously observed to be innately less susceptible in vitro to amphotericin B than other *Candida* species (4, 8). Goldman et al. have reported that a significantly better response to *C. krusei* infections is obtained for patients treated with amphotericin B doses of >1 mg/kg of body weight per day than for patients receiving lower doses (5). The clinical significance of in vitro resistance to amphotericin B still needs to be investigated further (8, 11, 24)

While our 1985–1986 survey indicated that 30% of *C. albicans* isolates were resistant to flucytosine, only 3% were found resistant in the present study. This phenomenon appears to be related to methodological factors. Eleven of 43 selected *C. albicans* isolates from our 1985 study were originally found resistant to flucytosine by a broth macrodilution method using yeast nitrogen base supplemented with 2% glucose (MIC, $\geq$100 μg/ml) (26). None of these was resistant when tested with the NCCLS M27-A microdilution method read at 48 h. However, 24-h MICs of $\geq$0.12 μg/ml observed in this study correlated well with MICs of $\geq$100 μg/ml obtained with the broth macrodilution method. Using this interpretative guideline, 23% of the *C. albicans* isolates from the present surveillance study would be considered resistant. New guidelines may be needed for the interpretation of this test, especially when read at 24 h.

It has been feared that the increased use of fluconazole for the treatment of candidiasis will lead to resistance or a shift toward intrinsically resistant non-*C. albicans* species (1, 12, 22). Resistance was first reported in AIDS patients with recurrent oropharyngeal candidiasis and is still seldom seen outside this patient group (22). A total of 302 patients in this study were treated with antifungal agents, and a majority (69%) received fluconazole either initially (55%) or following treatment amendment (14%). However, only two *C. albicans* isolates exhibited in vitro resistance to fluconazole (1%), consistent with the frequency reported in other North American studies (14, 15). Both of the affected patients had been treated with fluconazole before the onset of candidemia, suggesting acquired secondary resistance.

The interpretation of fluconazole and itraconazole susceptibility tests is often complicated by the occurrence of trailing growth. This phenomenon will influence the outcome of the tests depending on whether the incubation period is 24 or 48 h. Although the NCCLS method presently recommends a 48-h incubation period, there is mounting evidence that this time period may lead occasionally to an overestimation of MICs and that 24-h results correlate better with clinical outcome (10, 18, 19, 27). Using the NCCLS reference broth microdilution method with spectrophotometric reading, important differences due to trailing growth were observed between results obtained at 24 h and those obtained at 48 h, especially with *C. albicans* and *C. tropicalis* (25). Our clinical data indicate that 24-h 50% turbidity decrease test results correlate with a history of previous exposure to azole antifungal agents. Also, out of nine patients with *C. albicans* isolates resistant to fluconazole at 48 h but susceptible at 24 h, eight responded to treatment with fluconazole as the sole medication, suggesting an overestimation of MICs at 48 h. Using our current method, we retested 43 *C. albicans* isolates from a 1985 prefluconazole era surveillance program (results not shown). Interestingly, 0 and 11.6% were resistant to fluconazole at 24 and 48 h, respectively, similar to results obtained in the present surveillance study (1 and 21%, respectively). The overestimation of MICs with a 48-h incubation period may prove to be more frequent when the broth microdilution method is read spectrophotometrically as opposed to interpreted visually. Trailing growth with a turbidity reading slightly above the 50% reduction in OD used as a breakpoint will result in a high MIC, whereas a visual reading will focus on the "point of prominent decrease in turbidity" used as the endpoint in the NCCLS method and may result in a lower MIC. Although major progress as been made in antifungal susceptibility testing, it is apparent that further adjustments regarding methodology and interpretation are still desirable and will have some impact on the frequency of resistance reported in surveillance studies.

Our results show that *C. albicans* remains the *Candida* species most frequently implicated in nosocomial candidiasis in Quebec, with an overall frequency of 54% and a slightly higher frequency of 58% in bloodstream infections. The frequency of isolation of non-*C. albicans* species is higher in patients treated with azoles before the onset of candidiasis than in patients without previous exposure to azoles (62 versus 46%). The present distribution data, compared with those of a 1985 sur-

vey, indicate a significant increase in the frequency of *C. glabrata* isolates. Despite the more frequent use of azoles, resistance to fluconazole in *C. albicans* remains rare, and the frequency of isolation of intrinsically azole-resistant *C. krusei* is low. Resistance of *C. albicans* to fluconazole appears to be associated with long-term treatment with this drug.

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