Candida Species, Genotypes and Antifungal Susceptibility of *Candida* Isolates from Blood Samples of Patients at the Largest Tertiary Care Hospital in Thailand During 1999-2002

SUPORN FOONGLADDA, DVM, PhD*,
PORNPHAN PETLUM, BSc*,
PIYAPORN SAKULMAIWATANA, MSc*,
NIRAN VANPRAPAR, MD, MSc**

Abstract

From 1999 to 2002, a total of 202 *Candida* isolates causing candidemia were recovered from 202 individual patients in the largest tertiary hospital in Bangkok, Thailand. *C. albicans* comprised 44.55 per cent of all isolates. Non-*albicans Candida* spp. isolates accounted for 55.45 per cent of all candidemia episodes and were primarily due to *C. tropicalis* (45%) followed by *C. parapsilosis* (6%), *C. glabrata* (4%), and *C. krusei* (0.5%). Non-*albicans Candida* spp appeared more frequently in children (59%). Regarding etiology, non-*albicans Candida* spp showed an increase (67%) in the year 2002. The distribution of *C. albicans* genotypes was as follows: genotype A, 71 per cent; genotype B, 26 per cent and genotype C, 3 per cent, with a similar susceptibility proportion to amphotericin B, fluconazole and itraconazole. All isolates of *C. albicans, C. tropicalis*, and *C. parapsilosis* were susceptible to fluconazole *in vitro*. Only 16.7-19.8 per cent of the isolates were resistant to itraconazole. A high proportion of *C. glabrata* isolates showed drugs resistance.

Key word : Candidemia, *Candida* species, Genotypes, Drug Susceptibility

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Candidemia is emerging as an important condition causing severe morbidity and mortality in hospitalized patients and is increasingly encountered particularly as a terminal event to underlying diseases (1-3). Many publication have reported on the distribution of *Candida* species and drug susceptibility in blood isolates. Both distribution and drug susceptibility vary between geographic regions or countries

* Department of Microbiology,
** Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

wehich may be due to differences in antifungal drug-prescribing habits[2-9]. Although, *Candida albicans* is the most commonly isolated organism from patients with candidosis, other species such as *C. tropicalis, C. glabrata, C. parapsilosis* and *C. krusei* have been documented. However, there have been an increasing number of reports describing atypical *C. albicans* strains and genetic subtypes of *C. albicans*[10-12].

Recent advances in molecular technology enable detailed analysis of the genetic diversity of *C. albicans*, and several groups of *C. albicans* strains have been genetically characterized and reported[10, 11]. Using polymerase chain reaction (PCR) to isolate the 25S rRNA gene region, *C. albicans* has been classified into 5 genotypes on the basis of the amplified PCR product length. Molecular typing of *C. albicans* has been used for epidemio-logical investigation to develop a rational infection control measures and to determine the association between genotype and antifungal drug susceptibility.

The main objectives of this study were to obtain data regarding the spectrum of pathogenic *Candida* species, along with their respective antifungal drug susceptibilities, and to study the distribution of *Candida albicans* genotypes and their respective antifungal susceptibilities associated with nosocomial *Candida* infection in Siriraj Hospital, the largest tertiary hospital in Bangkok.

MATERIAL AND METHOD

Clinical isolates and reference strains

The *Candida* species isolated from all 202 candidemia patients in Siriraj Hospital during the period January 1999-December 2002 were studied. Antifungal therapy was not used before collection of the first specimens. Clinical data was recorded and included age, sex, underlying condition and antifungal drugs received. The following reference strains of *C. albicans* and *C. dubliniensis* were used as reference control strains for genotyping: *C. albicans* ATCC 64124 (genotype A), *C. albicans* ATCC 38246 (genotype B), *C. albicans* Singapore 7 (genotype C), *C. dubliniensis* CBS 7987 (genotype D), and *C. albicans* IFM 49826 (genotype E). *Candida parapsilosis* ATCC 22019 was used as the reference strain for quality control of susceptibility testing.

Organism identification

All yeast isolates were identified as *C. albican* on the basis of their cultural and morphological characteristics which included colony color on a Candi Select plate (Sanofi Diagnostics, France), chlamydoconidia formation on cornmeal agar and germ-tube formation tests. Non-*albican Candida* spp were identified by carbohydrate assimilation and fermentation tests.

Genotyping of *C. albicans*

The genotype of the clinical isolate of *C. albicans* was determined by a DNA amplification technique using a specific PCR primer set which spans a transposable intron region in the 25S rRNA gene as described by McCullough et al[10]. The PCR primer pairs were CA-INT-L (5′-ATAAGGGAAGTCGGC AAAATAGTACC GGAT-3′) and CA-INT-R (5′-C CTTGGCTGTGGTTTCGCTAGATAGTAGAT-3′)[10].

A small quantity of cells from at least 5 colonies of each strain were taken by using a micropipette tip and suspended in 10 µl sterile distilled water in a microcentrifuge tube. This cell suspension was used as the DNA template in the PCR reaction.

The polymerase chain reaction (PCR) was performed in a 0.5-ml PCR centrifuge tube in a total volume of 50 µl. The PCR reactions mixture consisted of 5 µl of 10X PCR buffer (GibcoBRL, USA), 5 µl each of 10 µM primers (10 mM), 1.5 µl of 25 mM $MgCl_2$ (1.5 mM), 4 µl of dNTP mixture (20 µM each dATP, dCTP, dGTP and dTTP) (GibcoBRL, USA), 0.5 µl of Taq DNA polymerase (2.5 U) (GibcoBRL, USA) and 2 µl of yeast cell suspension. The PCR was performed in a DNA thermal cycler (Perkin-Elmer Cetus Thermal cycler 480, USA). The amplifying conditions for the samples were incubation at 94°C for 3 min prior to 30 cycles at 94°C for 1 min, 65°C for 1 min and 72°C for 2.5 min, and a final extension at 72°C for 10 min. The amplification products were characterized by 2 per cent agarose gel electrophoresis and ethidium bromide staining.

Genotypes of *C. albicans* were determined as A, B, C, D and E as described[10,11]. *C. albicans* genotype A and B gave specific PCR product of 450 bp and 840 bp, respectively. The strain that gave two PCR products at 450 bp and 840 bp was *C. albicans* genotype C. *C. dubliniensis* or *C. albicans* genotype D gave a PCR product of 1,080 bp. *C. albicans* genotype E gave a specific 1,400 bp PCR product. In order to assess that the *C. albicans* genotype C strains were not a mixed culture of genotype A and B, 5 individual colonies of the genotype C strains were used as the DNA template for each PCR reaction.

Antifungal susceptibility testing

The testing was performed for susceptibility to amphotericin B, fluconazole, and itraconazole by the broth microdilution method following the recommendations of The National Committee for Clinical Laboratory Standards (NCCLS) document M27-A[13].

Interpretative criteria for susceptibility were classified as resistant if the MIC to fluconazole was ≥ 64 μg/ml and the MIC to itraconazole was ≥ 1.0 μg/ml[13]. An amphotericin B MIC of > 1.0 μg/ml was interpreted as a resistant isolate[13].

Statistical analysis

The statistical analyses were calculated by using the SPSS 10.1 computer program. Comparison of species distribution and/or MIC distribution were made using the chi-square test in each group. The non-parametric Kruskal-Wallis test ($p < 0.05$) was used to determine the difference in MIC values between species and genotypes.

RESULTS

Patient population and clinical data

A total of 202 *Candida* isolates, these were collected from 115 male and 87 female patients ranging in age from 12 days to 89 years. The available data concerning the underlying diseases in 114 patients is shown in Table 1. Most of these patients had leukemia or lymphoma.

Candida species

The overall distribution of species is shown in Table 2. The dominant causes of infection in individuals were *C. albicans* (44.5%) and *C. tropicalis* (45%). A few infections were due to *C. parapsilosis* (6%), *C. glabrata* (4%) and *C. krusei* (0.5%). *C.*

Table 1. Clinical data for 202 patients with candidemia.

Patient characteristic	No.	%
Sex		
Males	115	59.2
Females	87	40.8
Age in years		
12 days -15 years	93	46.04
> 15-60 years	76	37.6
> 60-89 years	33	16.3
Underlying medical conditions [a]		
Leukemia and lymphoma	50	43.9
Diabetes	18	15.8
Solid organ malignant diseases	16	14.0
Human immunodeficiency virus infection	10	8.8
Systemic lupus erythrematosus	5	4.4
Aplastic anemia, β-thalassemia	4	3.5
Burn	4	3.5
Others	7	6.1

[a] Data was available for 114 patients.

Table 2. Species distribution of 202 *Candida* strains isolated from blood samples.

Species	By year (No)				Total					
	1999	2000	2001	2002	Children (n = 93)		Adults (n = 109)		Total (n = 202)	
					No.	%	No.	%	No.	%
C. albicans	37	19	23	11	38	40.9	52	47.7	90	44.5
C. tropicalis	36	18	19	18	44	47.3	47	43.1	91	45
C. parapsilosis	4	2	3	3	7	7.5	5	4.6	12	6
C. glabrata	2	2	3	1	3	3.2	5	4.6	8	4
C. krusei	0	0	1	0	1	1.1	0	0	1	0.5

Table 3. Genotype distribution of the 90 *C. albicans* strains

Group	No. of cases	No of strains in the following genotypes					
		A		B		C	
		No.	%	No.	%	No.	%
Children	38	26	68.4	11	28.9	1	2.6
Adults	52	38	73.1	12	23.1	2	3.8
Total	90	64	71.1	23	25.6	3	3.3

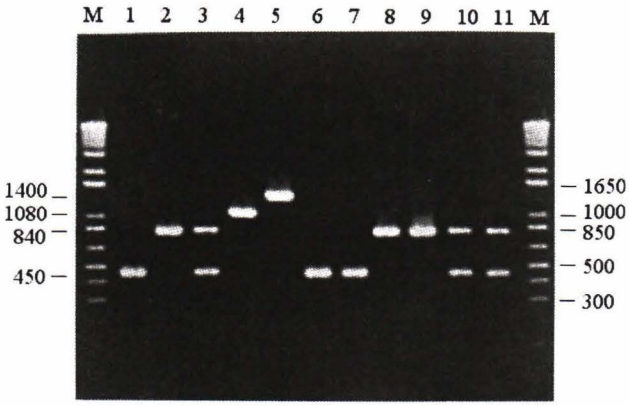

Fig. 1. Agarose gel electrophoresis of PCR products obtained from amplification of *C. albicans* different genotypes: lane M is 1 Kb plus DNA ladder bp marker; lane 1-5 are *C. albicans* reference strains genotype A, B, C, D and E of *C. albicans* ATCC 64124, ATCC 38246, ATCC Singapore 7, CBS7987 (*C. dublinien-sis*), and IFM 49826, respectively. Lane 6-7, 8-9 and 10-11 are clinical strains of genotype A, B, C, respectively.

albicans was the most commonly isolated species in adults (47.7%), whereas in children it was non-*albicans Candida* spp (59%). *C. parapsilosis* and *C. glabrata* caused 2-4 and 1-3 episodes of candidemia each year, respectively. The one *C. krusei* isolate was colleted from a child. Of the 10 patients who were HIV seropositive, 8 had *C. albicans* and 2 had *C. tropi-calis*.

The rank order of species over the three years period, 1999-2001, was relatively stable. The pro-portion of non- *albicans Candida* spp increased from 39-46 per cent in that 3 year period to 67 per cent in the year 2002.

Genotype of *Candida albicans* isolates

As shown in Fig. 1, *C. albicans* isolates were analyzed using a PCR method and classified into genotypes. The 90 clinical isolates of *C. albicans* were analyzed as 3 genotypes: genotype A was the most common genotype isolates (64 isolates, 71%), followed by genotype B (23 isolates, 25.6%), and genotype C (3 isolates, 3.3%). There was a stable pro-portion of genotype isolates during the 4 year period, as presented in Table 3. All 3 genotype C isolates

Table 4. *In vitro* susceptibilities of *Candida* spp to three antifungal agents.

Species	No. of isolates	No. and % isolates resistance					
		Amp B		Flu		Itra	
		No.	%	No.	%	No.	%
C. albicans	90	0	0	0	0	15	16.7
Geotype A	64	0	0	0	0	12	18.8
Geotype B	23	0	0	0	0	3	13
Geotype C	3	0	0	0	0	0	0
C. tropicalis	91	1	1	0	0	18	19.8
C. parapsilosis	12	1	8	0	0	2	16.7
C. glabrata	8	2	25	6	75	6	75
C. krusei	1	0	0	1	100	1	100

% percentage of resistance at a MIC, > 1 μg/ml for amphotericin B,
≥ 64 μg/ml for fluconazole, ≥ 1 μg/ml for itraconazole

were collected only in the year 1999. The distribution of genotypes in children and adults was similar.

Antifungal drugs susceptibility results

None of the *C. albicans* isolates in our study had amphotericin B MICs ≥ 2 μg/ml or fluconazole MICs ≥ 64 μg/ml (Table 4). The total of 5 *C. albicans* having a fluconazole MIC of 32 μg/ml were genotype A. Of this species isolates, 83 per cent had fluconazole MICs ≤ 8 μg/ml. Overall, 15 itraconazole resistant isolates were of genotypes A and B.

Only one of the *C. tropicalis* isolates and one of the *C. parapsilosis* isolates were resistant to amphotericin B at the MIC of 4 μg/ml. All of *C. tropicalis* isolates were susceptible to fluconazole and 86 per cent had MICs ≤ 8 μg/ml. All of the *C. parapsilosis* isolates were susceptible to fluconazole at MICs of ≤ 8 μg/ml. For itaconazole, 19.8 per cent and 16.7 per cent of *C. tropicalis* and *C. parapsilosis* respectively were resistant isolates.

Two of 8 *C. glabrata* isolates were resistant to amphotericin B (MIC,4 μg/ml), while 6 isolates were resistant to fluconazole and itraconazole. The *C. krusei* isolate showed intrinsic resistance to fluconazole and itraconazole at the MICs of 64 and 4 μg/ml, respectively, and susceptible to amphotericin B at the MIC of 1 μg/ml.

There was no significant change in the MICs of these three drugs for *Candida* spp during 1999 to 2002.

DISCUSSION

The results demonstrated that, *C. albicans* remains the most commonly isolated species in adults with cadidemia, at 48 per cent of all *Candida* isolates. This is the same trend demonstrated in many other reports[2,3,9]. However, a higher frequency of non-*C. albicans* isolates was noticed in this study among pediatric patients with candidemia, at 59 per cent of all isolates, of which *C. tropicalis* (47%) was the predominant species. *C. dubliniensis* was not identified in any of the blood specimens.

It seems that non-*C. albicans* species have different distributions in different climates geographic area or racial groups. The distribution of *Candida* spp in our study differs from that reported in other studies (Table 5)[3,9,14-18]. Similar observations have been reported in India i.e., that the most frequently identified isolates from candidemia patients were *C. tropicalis* (36-66%)[19,20]. *C. tropicalis* was also the second most commonly isolated *Candida* spp from vaginitis

Table 5. *Candida* species distribution of candidemia compared to prevalence in other reports.

Species	% of isolates by species									
	This study n = 202	USA n = 589	Canada n=422	Europe n = 302	Latin n = 103	Brazil n = 145	Saudi Arabia n = 68	Singapore n = 72	Taiwan n = 1,095
Year of observation	1999-2002	1997-1999	1996-1998	1997-1999	1999-2001	1995-1996	1996-2000	2001	1994-2000
C. albicans	44.5	55	54	58	42	37	54	34	50
C. not- *albicans*									
C. tropicalis	45	9	9	7	24	24	24	22	21
C. parapsilosis	6	11	12	19	21	25	9	9	14
C. glabrata	4	21	15	10	8	4	4	15	12
C. krusei	0.5	2	3	1	0	1	2	3	2
Other species	0	2	7	5	5	9	7	7	2

and pediatric oral candidosis, 34 per cent and 25 per cent respectively, in this laboratory.

Among the different genotypes of *C. albicans*, the frequency of genotypes A and B (71.1% and 25.6%, respectively) was not significantly higher than those identified in Japan (57% and 21.9%, respectively). The distribution of genotype C (3.3%) in this study was lower than that identified in Japan (18.6%) ($p = 0.001$)[11]. Those Japanese genotype results were from stock isolates from non-specific specimens strains but the isolates used in this study were all pathogenic strains. This might suggest that the genotype distribution is different in each area and that genotype C may not be as pathogenic as genotype A or B. However, MICs of the isolates did not correlated with this genotyping.

In the present study, all of the *C. albicans, C. tropicalis* and *C. parapsilosis* isolates were susceptible to fluconazole. None of the *C. albicans* isolates were found to be resistant to amphotericin B. Of the 91 *C. tropicalis* isolates all were sensitive to fluconazole. Whereas, St-Germain et al have published a percentage of *C. tropicalis* isolates resistant to fluconazole and itraconazole (11 of 41, 27% and 13 of 41, 32%, respectively) that is higher than found this study (0% and 20%, respectively) ($p < 0.05$)[3].

Of particular interest is the resistance of *C. glabrata* isolates to antifungal drugs; 75 per cent of the isolates demonstrated resistance to both fluconazole and itraconazole. The pattern of drug resistance of *C. glabrata* isolates differs widely with a report from Pfaller in 2001[9] that showed resistant *C. glabrata* in 0 and 58 per cent of isolates repectively, and a report from St-Germain in 2001[3] that showed resistant *C. glabrata* in 6.7 and 34.6 per cent of the isolates for fluconazole and itraconazole respectively[3,13]. It has been suggested that *C. glabrata* strains in the author's geographic area might be genetically different from the strains in the aforementioned reports. Fluconazole and itraconazole appeared to be less active against isolates of *C. glabrata.*

Nosocomial candidemia in the author's tertiary hospital is predominantly caused by non-*albicans* species, especially *C. tropicalis,* that are non-fluconazole resistant. Further investigations are necessary to elucidate the mechanisms involved in the increasing incidence of candidemia due to non-*C. albicans* infections. Pursuing the correlation between genotype subgroups and drugs susceptibility might render more information on this topic in the future.

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แคนดิดาสปีชีส์ จีโนทัยป์และความไวต่อยา ของแคนดิดาที่เพาะได้จากตัวอย่างเลือดของผู้ป่วยในโรงพยาบาลทุติยภูมิใหญ่ที่สุดในประเทศไทย ในปี พ.ศ. 2542–2545

ศุภร ฟุ้งลัดดา, สพบ, ปรด, ปิยาภรณ์ สกุลใหม่วัฒนา, วทม*,*
พรพรรณ เพชรล้ำ, วทบ, นิรันดร์ วรรณประภา, พบ, วทม***

ในปี พ.ศ. 2542–2545 เชื้อ*แคนดิดา* จำนวนทั้งสิ้น 202 สายพันธุ์ ที่เป็นสาเหตุของการติดเชื้อในกระแสเลือดเพาะได้จากเลือดผู้ป่วย 202 ราย ในโรงพยาบาลทุติยภูมิใหญ่ที่สุดในประเทศไทย ร้อยละ 44.55 เป็น*แคนดิดา อัลบิแคนส์ แคนดิดาที่ไม่ใช่อัลบิแคนส์* พบเป็นร้อยละ 55.45 โดยที่พบมากคือ *แคนดิดา ทรอพพิคาลิส* (ร้อยละ 45) ตามด้วย *แคนดิดา พาแรพสิโลสิส* (ร้อยละ 6) *แคนดิดา กลาบราตา* (ร้อยละ 4) และ*แคนดิดา ครูสิอัย* (ร้อยละ 0.5) *แคนดิดาสปีชีส์ที่ไม่ใช่อัลบิแคนส์* พบมากว่าในผู้ป่วยเด็ก (ร้อยละ 59) ในปี 2546 พบว่าเชื้อสาเหตุเป็น*แคนดิดาสปีชีส์ที่ไม่ใช่อัลบิแคนส์*เพิ่มสูงขึ้น (ร้อยละ 67) การกระจายของ *แคนดิดา อัลบิแคนส์* จีโนทัยป์พบดังนี้ ร้อยละ 71 เป็น จีโนทัยป์ เอ ร้อยละ 26 เป็น จีโนทัยป์ บี และ ร้อยละ 3 เป็น จีโนทัยป์ ซี โดยมีค่าความไวต่อยาแอมโฟเทอริซินบี ยาฟลูโคนาโซล และยาไอทราโคนาโซลไม่แตกต่างกันในแต่ละจีโนทัยป์ ทุกสายพันธ์ของ*แคนดิดาอัลบิแคนส์ แคนดิดาทรอพพิคาลิส* และ*แคนดิดาพาแรพสิโลสิส* ไวต่อยาฟลูโคนาโซลในหลอดทดสอบ มีเพียงร้อยละ 16.7–19.8 ที่ดื้อยาไอทราโคนาโซล สายพันธุ์ที่เป็นสปีชีส์*กลาบราตา* มีสัดส่วนการดื้อยาสูง

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ศุภร ฟุ้งลัดดา, ปิยาภรณ์ สกุลใหม่วัฒนา,
พรพรรณ เพชรล้ำ, นิรันดร์ วรรณประภา
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* ภาควิชาจุลชีววิทยา,

** ภาควิชากุมารเวชศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10700