Twelve years of fluconazole in clinical practice: global trends in species distribution and fluconazole susceptibility of bloodstream isolates of *Candida*

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ABSTRACT

We determined the species distribution and in-vitro susceptibility of 6082 bloodstream infection (BSI) isolates of *Candida* spp. collected from 250 medical centres in 32 nations over a 10-year period from 1992 through 2001. The species included 3401 *C. albicans*, 984 *C. glabrata*, 796 *C. parapsilosis*, 585 *C. tropicalis*, 153 *C. krusei*, 67 *C. lusitaniae*, 48 *C. guilliermondii*, 10 *C. famata*, 10 *C. kefyr*, six *C. pelliculosa*, five *C. rugosa*, four *C. lipolytica*, three *C. dubliniensis*, three *C. inconspicua*, two *C. sake* and one isolate each of *C. lambica*, *C. norvegensis* and *C. zeylanoides*. Minimum inhibitory concentration determinations were made using the National Committee for Clinical Laboratory Standards reference broth microdilution method. Variation in the rank order and frequency of the different species of *Candida* was observed over time and by geographic area. The proportion of BSI due to *C. albicans* and *C. glabrata* increased and *C. parapsilosis* decreased over time in Canada, the USA and Europe. *C. glabrata* was an infrequent cause of BSI in Latin America and the Asia-Pacific region. Very little variation in fluconazole susceptibility was observed among isolates of *C. albicans*, *C. tropicalis* and *C. parapsilosis*. These species accounted for 78% of all BSI and remained highly susceptible (91–100% susceptible) to fluconazole from 1992 to 2001 irrespective of geographic origin. The prevalence of fluconazole resistance among *C. glabrata* isolates was variable both over time and among the various countries and regions. Resistance to fluconazole among *C. glabrata* isolates was greatest in the USA and varied by US census region (range 0–23%). These observations are generally encouraging relative to the sustained usefulness of fluconazole as a systemically active antifungal agent for the treatment of candida BSI.

Keywords Candidemia, surveillance, fluconazole

Clin Microbiol Infect 2004; 10 (Suppl. 1): 11–23

INTRODUCTION

Candidemia is without question the most important of the invasive mycoses [1]. It is estimated that bloodstream infection (BSI) due to *Candida* spp. occurs at a rate of 0.5–10 infections per 1000 hospital admissions and accounts for 8–10% of all nosocomial BSI [2–5]. Population-based studies conducted in the USA estimate an annual incidence of 6–10 episodes of candidemia per 100 000 population [6–9]. This relatively high incidence, plus an excess mortality of approximately 38% [10], makes BSI due to *Candida* spp. an important public-health problem [1].

Treatment of candidemia over the past decade has been enhanced considerably by the introduction of fluconazole in 1990 [11,12]. The absence of toxicity, ease of administration, and documented efficacy in treatment of candidemia have resulted in extensive usage of fluconazole in most areas of the world [11–15]. Because of this widespread usage, concern about the possible development of fluconazole resistance among *Candida* spp. abounds [15–21]. Fluconazole resistance has clearly been documented among *Candida* spp. isolated from patients with acquired immune deficiency syndrome who have recurrent oropharyngeal

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candidiasis [19,22–24]; however, it is relatively uncommon among most species causing BSI [8,11,17,25–27]. The exception to this statement is *C. glabrata*, of which ≥10% of BSI isolates may be highly resistant to fluconazole [6,8,9,28–31]. Suboptimal fluconazole dosing practices [low dose (< 400 mg/day), poor indications] may lead to an increased frequency of isolation of *C. glabrata* as an aetiological agent of candidemia in hospitalised patients [30,32,33] and possibly to increased fluconazole (and other azole) resistance secondary to induction of CDR efflux pumps [21,29,30,34]. Given these concerns, surveillance of candida BSI to detect changes in species distribution and susceptibility to fluconazole on a regional, national and international scale is warranted [30,35,36].

One of the important aspects of any antimicrobial resistance surveillance programme is longitudinality [27,30,37,38]. By conducting surveillance of specific pathogens over time one can assess the emergence of specific strains [39,40] or species [27] and also detect changes in the antimicrobial susceptibility profile of the organisms [30,37]. Furthermore, when longitudinal surveillance encompasses a broad geographic distribution, one may eventually develop a useful picture of regional, national or even global trends in species distribution and antimicrobial resistance [30,37,38].

The number of surveillance programmes that focus on candidemia has increased in recent years [30]. These programmes have generated important information concerning the emergence, or absence thereof, of *Candida* species other than *C. albicans*, as well as antifungal susceptibility data determined by standardised testing methods [20,30]. Unfortunately, most programmes have not been functional long enough to provide longitudinal data that also encompasses isolates from diverse geographic settings [30]. At the University of Iowa we have conducted surveillance of candida BSI using a consistent protocol (consecutive incident BSI isolates, one per patient, multiple institutions) and standardised reference quality identification and antifungal susceptibility testing methods from 1992 up to the present [30,33]. This cumulative experience allows us to examine changes in species distribution and in-vitro susceptibility to fluconazole of candida BSI isolates spanning a 10-year period and representing 250 medical centres in 32 nations.

CANDIDA BLOODSTREAM INFECTION SURVEILLANCE AT THE UNIVERSITY OF IOWA

Organism collection

A total of 6082 BSI isolates of *Candida* spp. from 250 medical centres in 32 nations were submitted to the University of Iowa College of Medicine (Iowa City, IA, USA) for identification and antifungal susceptibility testing of fluconazole between 1992 and 2001. The number of isolates submitted each year ranged from 133 to 2770 (Table 1). The isolates represented consecutive incident isolates from patients with candidemia

Table 1. Species distribution of candida bloodstream isolates by year: 1992–2001[a]

	% of isolates by year									
Species	**1992**	**1993**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**All years**
No. tested	235	315	332	133	413	328	320	1236	2770	6082
C. albicans	44.3	45.4	53.3	52.6	54.0	55.2	54.7	54.4	59.8	55.9
C. glabrata	16.6	14.0	20.5	15.8	15.3	17.7	15.3	15.3	16.4	16.2
C. parapsilosis	21.7	24.4	9.0	10.5	18.9	14.3	10.3	13.8	10.7	13.1
C. tropicalis	11.9	12.4	11.4	15.8	7.0	8.5	11.9	11.8	7.9	9.6
C. krusei	2.6	1.3	4.2	3.0	1.7	1.2	2.8	2.5	2.7	2.5
C. lusitaniae	2.1	0.6	0.6	0.0	0.0	0.6	2.2	1.1	1.3	1.1
C. guilliermondii	0.4	1.3	0.4	0.0	1.9	2.1	0.9	0.4	0.6	0.8
Other spp.[b]	0.4	0.6	0.6	2.3	1.2	0.4	1.9	0.7	0.6	0.8

[a]Includes the following geographic areas: Asia-Pacific (441 isolates), Europe, including Israel and Turkey (775 isolates), Latin America (560 isolates), Canada (623 isolates), and USA (3683 isolates).
[b]Includes *C. famata* (10 isolates), *C. kefyr* (10 isolates), *C. pelliculosa* (six isolates), *C. lipolytica* (four isolates), *C. rugosa* (five isolates), *C. dubliniensis* (three isolates), *C. inconspicua* (three isolates), *C. sake* (two isolates) and one isolate each of *C. lambica*, *C. norvegensis* and *C. zeylanoides*.

cared for at hospitals in the following geographic regions (Table 2): Asia Pacific (441 isolates from 17 sites), Europe, including Israel and Turkey (775 isolates, 40 sites), Latin America (560 isolates, 18 sites), Canada (623 isolates, eight sites) and the USA (3683 isolates, 167 sites). The US contributing sites represented all nine US Bureau of the Census regions (Table 3 and Fig. 1): region 1, Pacific (439 isolates); region 2, Mountain (261 isolates); region 3, West North Central (302 isolates); region 4, West South Central (162 isolates); region 5, East North Central (376 isolates); region 6, East South Central (94 isolates); region 7, New England (83 isolates); region 8, Mid-Atlantic (736 isolates); and region 9, South Atlantic (1230 isolates). The isolates included *C. albicans* (3401 isolates), *C. glabrata* (984 isolates), *C. parapsilosis* (796 isolates), *C. tropicalis* (585 isolates), *C. krusei* (153 isolates), *C. lusitaniae* (67 isolates), *C. guilliermondii* (48 isolates), *C. famata* (10 isolates), *C. kefyr* (10 isolates), *C. pelliculosa* (six isolates), *C. lipolytica* (four isolates), *C. rugosa* (five isolates), *C. dubliniensis* (three isolates), *C. inconspicua* (three isolates), *C. sake* (two isolates) and one isolate each of *C. lambica*, *C. norvegensis* and *C. zeylanoides*. All isolates were identified by Vitek and API

Table 2. Species distribution of candida bloodstream isolates by geographic area: 1992–2001

Area	No. sites	No. isolates	% Isolates by species					
			CA	*CG*	*CP*	*CT*	*CK*	Other[a]
Asia-Pacific	17	441	73.5	10.2	8.4	3.9	3.2	0.8
Australia	4	44	65.9	6.8	15.9	4.6	6.8	0.0
China	2	28	50.0	21.4	3.6	21.4	0.0	3.6
Japan	1	2	100.0	0.0	0.0	0.0	0.0	0.0
Malaysia	1	35	28.6	5.7	48.6	14.3	2.8	0.0
Singapore	1	1	0.0	100.0	0.0	0.0	0.0	0.0
S. Africa	8	331	81.3	10.0	3.6	1.2	3.0	0.9
Europe	40	775	57.6	12.9	14.1	7.5	3.4	4.5
Austria	1	4	100.0	0.0	0.0	0.0	0.0	0.0
Belgium	1	10	70.0	10.0	10.0	0.0	0.0	10.0
Czech Republic	2	46	78.3	6.5	4.4	6.5	4.3	0.0
France	5	83	60.2	20.5	3.6	6.0	7.2	2.5
Germany	4	73	45.2	24.7	16.4	8.2	1.4	4.1
Greece	1	4	75.0	25.0	0.0	0.0	0.0	0.0
Ireland	1	1	100	0.0	0.0	0.0	0.0	0.0
Israel	1	86	45.4	9.3	18.6	22.1	1.2	3.4
Italy	7	99	69.7	7.1	11.1	5.1	2.0	5.0
The Netherlands	2	30	56.7	23.3	10.0	6.7	0.0	3.3
Poland	1	3	0.0	0.0	33.3	33.3	0.0	33.4
Portugal	1	28	42.9	14.3	21.4	10.7	3.6	7.1
Slovakia	1	22	68.2	9.1	9.1	0.0	13.6	0.0
Spain	3	86	47.7	16.3	24.4	2.3	3.5	5.8
Sweden	1	9	77.8	11.1	11.1	0.0	0.0	0.0
Switzerland	1	29	79.3	13.8	0.0	6.9	0.0	0.0
Turkey	3	150	55.3	6.7	18.7	6.7	4.0	8.6
UK	4	12	50.0	25.0	16.7	0.0	8.3	0.0
Latin America	18	560	46.6	7.5	17.7	21.3	3.6	3.3
Argentina	4	79	43.0	6.3	27.9	21.5	0.0	1.3
Brazil	6	279	44.8	7.5	20.4	21.5	2.9	2.9
Chile	2	82	61.0	12.2	9.8	13.4	0.0	3.6
Colombia	2	9	33.3	0.0	22.2	33.3	0.0	11.2
Mexico	3	13	53.8	0.0	30.8	15.4	0.0	0.0
Venezuela	1	98	42.9	6.1	6.1	25.6	12.2	6.2
Canada	8	623	58.9	20.1	10.3	5.9	2.4	2.4
USA	167	3683	54.4	18.3	13.2	9.6	2.1	2.4
Total	250	6082	55.9	16.2	13.1	9.6	2.5	2.7

[a]Includes *C. famata* (10 isolates), *C. kefyr* (10 isolates), *C. pelliculosa* (six isolates), *C. lipolytica* (four isolates), *C. rugosa* (five isolates), *C. dubliniensis* (three isolates), *C. inconspicua* (three isolates), *C. sake* (two isolates) and one isolate each of *C. lambica*, *C. norvegensis*, and *C. zeylanoides*.

Table 3. Species distribution of candida bloodstream isolates in each of the nine US Bureau of the Census regions

	% of isolates by US census region									
Species	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**All**
No. tested	439	261	302	162	376	94	83	736	1230	3863
C. albicans	48.7	64.5	60.6	56.8	47.6	61.7	47.0	51.1	56.4	54.4
C. glabrata	18.5	15.3	18.9	11.7	26.3	18.0	37.3	18.8	15.5	18.3
C. parapsilosis	18.5	4.6	7.6	13.6	10.7	4.3	9.7	17.1	13.9	13.2
C. tropicalis	9.6	8.8	10.6	9.9	9.3	11.7	4.8	8.7	10.3	9.6
C. krusei	2.5	1.1	0.7	5.6	3.7	4.3	1.2	1.9	1.6	2.1
C. lusitaniae	1.6	2.7	0.9	1.2	2.4	0.0	0.0	1.2	0.9	1.3
C. guilliermondii	0.6	1.5	0.0	0.0	0.0	0.0	0.0	0.5	0.5	0.5
Other species[a]	0.0	1.5	0.7	0.6	0.0	0.0	0.0	0.7	0.9	0.6

[a]Includes *C. famata* (10 isolates), *C. kefyr* (10 isolates), *C. pelliculosa* (six isolates), *C. lipolytica* (four isolates), *C. rugosa* (five isolates), *C. dubliniensis* (three isolates), *C. inconspicua* (three isolates), *C. sake* (two isolates) and one isolate each of *C. lambica*, *C. norvegensis*, and *C. zeylanoides*.

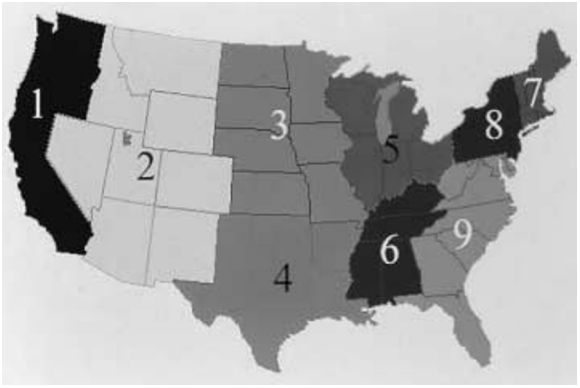

Fig. 1. Map indicating the nine US Bureau of the Census regions.

products (bioMerieux, St Louis, MO), supplemented by conventional methods as required [41], and were stored as water suspensions until they were used. Prior to testing, each isolate was passaged at least twice on potato dextrose agar (Remel, Lenexa, KS) to ensure purity and viability.

Antifungal susceptibility studies

Broth microdilution testing was performed in accordance with the guidelines in National Committee for Clinical Laboratory Standards (NCCLS) document M27-A [42]. Fluconazole was obtained from the manufacturer (Pfizer Pharmaceutical Group, New York, NY) as a standard reagent grade powder. The final concentrations of fluconazole ranged from 0.12 to 128 μg/mL. The trays were incubated in air at 35 °C and minimum inhibitory concentration (MIC) endpoints were read after 48 h incubation.

Following incubation, the broth microdilution wells were read with the aid of a reading mirror; the growth in each well was compared with that of the growth control (drug-free) well. The MICs of fluconazole were defined as the lowest concentration that produced a prominent decrease in turbidity (approximately 50% reduction in growth) compared with that of the drug-free control [42]. The interpretive criteria for fluconazole were those published by Rex *et al*. [43] and the NCCLS [42]: susceptible (S), MIC ≤8 μg/mL; susceptible-dose-dependent (S-DD), MIC 16–32 μg/mL; resistant (R), MIC ≥ 64 μg/mL.

GLOBAL TRENDS IN SPECIES DISTRIBUTION AND FLUCONAZOLE SUSCEPTIBILITY AMONG CANDIDA BSI ISOLATES

Temporal and geographic influences on species distribution in candidemia

Temporal distribution

Among the 6082 isolates of *Candida* submitted for testing from 1992 to 2001, 55.9% were *C. albicans*, 16.2% were *C. glabrata*, 13.1% were *C. parapsilosis*, 9.6% were *C. tropicalis*, 2.5% were *C krusei*, and 2.7% were miscellaneous *Candida* species (Table 1). The rank order of the different species varied slightly over time, although *C. albicans* was the predominant species in each year. *C. parapsilosis* was the most common non-*albicans* species in 1992 (21.7%) and 1993 (24.4%); however, the overall frequency of this species as a cause of BSI decreased to 9% in 1995 and, with the exception of 1997 (18.9%), remained less than

15% throughout the remainder of the study period. *C. glabrata* accounted for between 14.0% and 20.5% of BSI during the 10-year period and although there was no demonstrable trend towards an increase in the overall percentage of BSI due to this species over time, it rose from the third most common BSI isolate in 1992 and 1993 to the second most common from 1995 through 2001. The frequency of *C. tropicalis* and *C. krusei* as BSI isolates did not show any trend towards an increase or decrease over time. Notably, the overall frequency of *C. krusei* as a cause of BSI remained low at 2.5% (range 1.2–4.2%) for the 10-year period.

Geographic distribution

The frequencies of BSI due to the various species of *Candida* in the different geographic areas are shown in Table 2. The frequency of *C. albicans* as a cause of BSI ranged from 46.6% in Latin America to 73.5% in the Asia-Pacific region. Within each of the major geographic areas the frequency of BSI due to *C. albicans* varied considerably, ranging from 28.6% (Malaysia) to 81.3% (South Africa) in the Asia-Pacific region, from 45.2% (Germany) to 79.3% (Switzerland) in Europe, and 33.3% (Colombia) to 61.0% (Chile) in Latin America. Over the 10-year period the frequency of *C. albicans* increased from 44% to 58% in the USA, decreased from 70% to 51% in Canada, and remained unchanged in the other geographic areas (data not shown).

C. glabrata was least common as a cause of BSI in Latin America (7.5%, range 0.0% to 12.2%) and most common in Canada (20.1%) and the USA (18.3%). Although there was no overall trend towards an increase in the frequency of this species as a cause of BSI over time (Table 1), the frequency of BSI due to *C. glabrata* increased from 13% to 24% in Canada, from 11% to 13% in Europe, and from 14% to 18% in the USA during the 10-year period (data not shown).

C. parapsilosis was more common than *C. glabrata* as a cause of BSI in the European and Latin American regions and was the third most common species in Asia-Pacific, Canada and the USA. *C. parapsilosis* was the most common BSI isolate in Poland (33.3%) and Malaysia (48.6%). The frequency of *C. parapsilosis* as a cause of BSI decreased over time in Canada (18% to 8%), Europe (20% to 11%), Latin America (45% to 13%) and the USA (24% to 11%).

Although *C. tropicalis* was the fourth most common species overall (Table 1), it was equal to or more common than *C. glabrata* and *C. parapsilosis* in China, the Czech Republic, Poland, Israel, Brazil, Chile, Colombia and Venezuela (Table 2). *C. tropicalis* was the second most common BSI isolate overall in Latin America (21.3%) and the frequency of this species as a cause of BSI in Latin America increased from 10% to 24% over the course of the study.

C. krusei was not a common cause of BSI in most study sites; however, it accounted for more than 10% of BSI in Slovakia (13.6%) and Venezuela (12.2%) and was more common than *C. tropicalis* in Australia, South Africa, France, Slovakia, Spain and the United Kingdom. *Candida krusei* did not appear to be increasing over time in any of the areas studied.

Species distribution among the nine US census regions

Although several surveillance studies of candidemia have been conducted in the USA, they have generally not been regionally comprehensive or longitudinal [3,4,6,8,9,16,18]. Given the variation in species distribution among candida BSI within the broad geographic areas noted in Table 2 and among individual institutions reported previously [33], it is reasonable to assume that regional variation in species distribution and possibly fluconazole susceptibility, may exist among US candida BSI isolates. To address the paucity of published US regional surveillance data we have stratified the 3683 US BSI isolates in the present study according to the location of the submitting institution in each of the nine US Bureau of the Census regions (Table 3). A great deal of variation in species distribution among candida BSI isolates was noted among the nine US census regions. *C. albicans* was the predominant species in all regions; however, it accounted for less than 50% of all candida BSI in region 1 (Pacific, 48.7%), region 5 (East North Central, 47.6%) and region 7 (New England, 47.0%) and for 60% or greater in region 2 (Mountain, 64.5%), region 3 (West North Central, 60.6%) and region 6 (East South Central, 61.7%). *C. glabrata* was the second most common species in all regions with the exception of region 4 (West South Central) where it was superseded by *C. parapsilosis*. The highest frequency of *C. glabrata* causing BSI was observed in region 7 (New England, 37.3%) and the lowest was in region 4 (West South Central, 11.7%).

C. parapsilosis was the second most common BSI isolate in regions 1 (Pacific; tied with *C. glabrata* at 18.5%) and 4 (West South Central), the third most common in regions 5 (East North Central), 7 (New England), 8 (Mid-Atlantic) and 9 (South Atlantic), and the fourth most common in regions 2 (Mountain), 3 (West North Central) and 6 (East South Central). *C. tropicalis* accounted for approximately 10% of candida BSI in all regions with the exception of region 7 (New England, 4.8%). It was either the third or fourth ranked species in all nine regions. *C. krusei* was the fifth most common species overall in the USA, ranging from 0.7% of BSI in region 3 (West North Central) to 5.6% in region 4 (West South Central).

Trends in fluconazole susceptibility in relation to time, geographic location and species of Candida in candidemia

Variation in fluconazole susceptibility by species and by year

The fluconazole susceptibility profile of all 6082 isolates of *Candida* spp. was 90% S, 7% S-DD and 3% R with little variation over the 10-year period (Table 4). A persistent and high level of susceptibility to fluconazole was observed for *C. albicans* (89–100% S, 0–9% R), *C. parapsilosis* (93–100% S, 0–2% R) and *C. tropicalis* (91–100% S, 0–9% R). No trend toward greater resistance to fluconazole was observed among these species over time.

Although *C. glabrata* was the least susceptible to fluconazole among the four most common species of *Candida* causing BSI (61.4% S vs. 97.8–98.6% S), a shift towards increased susceptibility from 1992 (15% S, 18% R) to 2000 (83% S, 5% R) was observed. Although fluconazole susceptibility decreased somewhat in 2001 (64% S), the per cent R remained low at 7%. This shift was observed in all of the geographic areas and represented not only an increase in the per cent S but a decrease in the per cent R as well (Table 4).

Fluconazole susceptibility by geographic area and by species

The overall susceptibility of candida BSI isolates was greater than 90% for all geographic areas (91–94% S, 2–3% R) with the exception of the USA (88% S, 4% R) (Table 5). A high degree of susceptibility was observed in all areas for *C. albicans* (98–100% S, 0–2% R), *C. parapsilosis* (98–100% S, 0–1% R) and *C. tropicalis* (94–100% S, 0–1% R). Fluconazole susceptibility among BSI isolates of *C. glabrata* was highest in the Asia-Pacific region (76%) and lowest in the USA (58% S). Rates of resistance among *C. glabrata* ranged from 9% in the USA and Latin America to 2% in the Asia-Pacific region.

Fluconazole susceptibility by US census region

Among the 3683 candida BSI isolates from the USA, fluconazole susceptibility ranged from 85% to 91% and resistance ranged from 1% to 5% among the nine US census regions (Table 6). *C. albicans*, *C. parapsilosis* and *C. tropicalis* were all highly susceptible to fluconazole (94–100% S, 0–3% R) with very little variation among the different regions. Fluconazole susceptibility of *C. glabrata* BSI isolates varied considerably among the nine US census regions. Susceptibility was lowest in region 1 (Pacific, 38%) and region 6 (East South Central, 47%) and highest in region 4 (West South Central, 84%). The prevalence of fluconazole resistance among *C. glabrata* was lowest in region 7 (New England, 0%) and was highest in region 6 (East South Central, 23%). Interestingly, there was little relationship between the frequency of *C. glabrata* BSI in a given region and the susceptibility of the isolates to fluconazole. The most susceptible isolates were observed in the regions with the lowest (region 4, 11.7%; 84% S, 5% R) and the highest (region 7, 37.3%; 71% S, 0% R) frequency of *C. glabrata* BSI isolates. Notably, the three regions with the highest prevalence of resistance to fluconazole (regions 6, 8 and 9; 23%, 14% and 10% R, respectively) were contiguous in the Southeast portion of US (Fig. 1).

SUMMARY AND DISCUSSION OF SURVEILLANCE DATA AND SUGGESTIONS FOR FUTURE INVESTIGATION

In this study we demonstrate important variations in the rank order and frequency of the various species of *Candida* causing BSI over time and by geographic area. An important observation was the high frequency of *C. albicans* as a cause of BSI in many areas of the world. *C. albicans* accounted for >60% of BSI in 14 of the 32 nations included in this study. Likewise,

Table 4. Fluconazole susceptibility over 10 years, 1992–2001[a]

Species	Year	No. tested	Cumulative percentage susceptible at MIC (μg/mL)										
			0.12	0.25	0.5	1	2	4	8	16	32	64	128
C. albicans	1992	104	2	56	91	97	99	100	100[b]				
	1993	143	5	62	90	96	98	98	98[b]	98	98	98	99
	1995	177	16	61	78	83	86	89	89[b]	91	91	92	92
	1996	70	11	54	67	86	97	99	99[b]	99	99	99	99
	1997	223	26	78	91	96	98	99	99[b]	99	99	99	99
	1998	181	39	87	95	97	98	98	98[b]	99	99	99	99
	1999	175	33	93	99	100	100	100	100[b]				
	2000	672	25	91	96	97	97	98	98[b]	99	99	99	99
	2001	1656	14	80	94	98	99	99	99[b]	99	99	99	99
C. glabrata	1992	39	0	0	0	0	0	3	15[b]	59	82	85	92
	1993	44	0	0	0	2	9	11	16[b]	75	89	93	98
	1995	68	0	3	6	7	7	15	49[b]	82	85	90	96
	1996	21	0	0	0	10	10	10	14[b]	86	86	86	91
	1997	63	0	0	0	2	3	19	46[b]	89	92	97	98
	1998	58	0	2	2	2	19	41	66[b]	91	95	95	100
	1999	49	2	2	4	6	37	71	84[b]	94	96	98	100
	2000	189	1	1	1	4	21	56	83[b]	91	95	97	99
	2001	452	0	0	0	1	6	31	64[b]	91	93	95	99
C. parapsilosis	1992	51	0	4	35	71	94	98	98[b]	98	98	100	
	1993	77	0	5		30	60	92	96[b]	99	100		
	1995	30	0	3	43	63	83	87	93[b]	100			
	1996	14	0	14	50	64	93	93	93[b]	100			
	1997	78	3	19	64	82	96	99	100[b]				
	1998	47	0	19	66	92	98	100	100[b]				
	1999	33	0	24	67	91	97	100	100[b]				
	2000	170	0	11	51	83	92	98	100[b]				
	2001	296	0	5	43	79	92	96	99[b]	99	99	100	
C. tropicalis	1992	28	0	11	50	89	96	96	100[b]				
	1993	39	0	5	36	77	92	95	97[b]	97	97	97	97
	1995	38	5	16	61	87	95	95	95[b]	97	97	97	97
	1996	21	0	5	48	62	91	91	91[b]	91	91	91	91
	1997	29	0	31	45	83	97	100	100[b]				
	1998	28	0	43	75	93	96	96	100[b]				
	1999	38	11	48	90	90	95	95	97[b]	97	97	97	100
	2000	146	1	21	55	88	96	97	97[b]	99	100		
	2001	218	0	11	35	68	93	98	99[b]	99	100		
All species[c]	1992	235	1	27	55	70	78	80	83[b]	91	96	97	99
	1993	315	2	30	53	68	80	82	84[b]	93	96	98	99
	1995	332	9	35	54	61	67	71	78[b]	87	97	93	94
	1996	133	6	32	49	64	77	78	79[b]	93	93	96	96
	1997	413	14	48	64	73	79	83	89[b]	96	97	99	99
	1998	328	21	55	69	76	83	87	92[b]	97	99	99	99
	1999	320	20	61	75	79	85	92	94[b]	98	98	99	99
	2000	1236	14	54	67	77	82	88	93[b]	96	97	99	99
	2001	2770	8	50	65	74	79	85	91[b]	96	97	99	99
All organisms	All years	6082	11	48	64	73	79	85	90[b]	95	97	98	99

[a]Broth microdilution testing according to NCCLS M27-A [42].
[b]Percentage of isolates susceptible to fluconazole at the NCCLS breakpoint of ≤ 8 μg/mL.
[c]Includes *C. krusei* (153 isolates), *C. lusitaniae* (67 isolates), *C. guilliermondii* (48 isolates), *C. famata* (10 isolates), *C. kefyr* (10 isolates), *C. pelliculosa* (six isolates), *C. lipolytica* (four isolates), *C. rugosa* (five isolates), *C. dubliniensis* (three isolates), *C. inconspicua* (three isolates), *C. sake* (two isolates) and one isolate each of *C. lambica*, *C. norvegensis* and *C. zeylanoides*.

C. albicans was observed in >60% of BSI in three of the nine US census regions. *Candida albicans* remains the most important aetiological agent of candidemia worldwide.

C. glabrata also demonstrated an increase in frequency over time as a cause of BSI in Canada, the USA and in Europe, but was an infrequent cause of BSI in Latin America and the Asia-Pacific

Table 5. Fluconazole susceptibility by geographic area

Species	Area[b]	No. tested	Cumulative percentage inhibited at MIC (μg/mL)[a]										
			0.12	0.25	0.5	1	2	4	8	16	32	64	128
C. albicans	Asia-Pac.	324	9	76	93	98	99	99	99[c]	99	99	99	99
	L. Am.	261	23	89	99	99	99	99	100[c]				
	Europe	446	33	89	97	98	99	99	99[c]	99	99	99	99
	Canada	367	25	88	97	99	99	99	99[c]	99	99	99	100
	USA	2003	15	76	91	95	97	98	98[c]	98	98	98	99
C. glabrata	Asia-Pac.	45	0	0	0	0	2	44	76[c]	98	98	100	
	L. Am.	42	0	0	0	0	7	36	71[c]	88	91	93	98
	Europe	100	1	1	1	1	9	29	61[c]	94	97	98	99
	Canada	125	0	0	0	0	10	35	72[c]	91	94	98	98
	USA	671	0	1	1	3	13	34	58[c]	86	91	93	98
C. parapsilosis	Asia-Pac.	37	0	11	41	57	68	87	97[c]	97	97	100	
	L. Am.	99	2	10	43	67	85	98	100[c]				
	Europe	109	0	11	59	87	97	99	99[c]	100			
	Canada	64	0	8	56	86	94	98	100[c]				
	USA	487	0	9	45	78	95	97	98[c]	99	99	100	
C. tropicalis	Asia-Pac.	17	0	6	12	59	94	100	100[c]				
	L. Am.	119	1	16	46	81	96	97	99[c]	100			
	Europe	58	2	14	40	72	93	93	95[c]	98	100		
	Canada	37	0	27	49	81	100	100	100[c]				
	USA	354	1	19	53	80	94	97	98[c]	98	99	99	99
C. krusei	Asia-Pac.	14	0	0	0	0	0	0	7	14	71	100	
	L. Am.	20	0	0	0	0	0	0	5	10	60	100	
	Europe	26	0	0	0	0	0	8	12	23	42	96	100
	Canada	15	0	0	0	0	0	0	0	7	60	87	100
	USA	78	0	0	0	0	0	0	3	21	62	100	
All species[d]	Asia-Pac.	441	6	58	73	80	84	90	94[c]	97	98	99	99
	L. Am.	560	11	47	64	76	84	90	94[c]	96	98	99	99
	Europe	775	19	55	68	76	81	85	90[c]	96	97	99	99
	Canada	623	14	55	67	73	78	84	91[c]	96	98	99	99
	USA	3683	8	45	62	72	78	83	88[c]	95	96	98	99

[a]Broth microdilution testing according to NCCLS M27-A [42].
[b]Geographic areas: Asia-Pac, Asia-Pacific; USA, United States of America; L. Am., Latin America.
[c]Percentage of isolates susceptible to fluconazole at the NCCLS breakpoint of ≤ 8 μg/mL.
[d]Includes *C. lusitaniae* (67 isolates), *C. guilliermondii* (48 isolates), *C. famata* (10 isolates), *C. kefyr* (10 isolates), *C. pelliculosa* (six isolates), *C. lipolytica* (four isolates), *C. rugosa* (five isolates), *C. dubliniensis* (three isolates), *C. inconspicua* (three isolates), *C. sake* (two isolates) and one isolate each of *C. lambica*, *C. norvegensis* and *C. zeylanoides*.

region. The frequency of *C. glabrata* as a cause of BSI also varied widely among the nine USA census regions. The highest proportion of BSI due to *C. glabrata* overall was observed in New England (region 7, 37.3%).

In contrast to *C. albicans* and *C. glabrata*, *C. parapsilosis* appeared to be decreasing in frequency as a cause of BSI in many areas of the world including Canada, the USA, Latin America and Europe. However, *C. parapsilosis* remained a leading cause of BSI in several locations in Latin America, the Asia-Pacific region and in Europe. It was the most common cause of candida BSI in Malaysia (48.6%).

This study is the first to provide regional surveillance information on candida BSI in the USA. As noted above, significant variation in the frequency and rank order of the different species among the nine US census regions was observed, with the greatest variation seen with *C. glabrata* (Table 3).

Similar to the variation in species distribution on a regional, national and international basis was the variation in fluconazole susceptibility and resistance. Very little variation in fluconazole susceptibility was observed among BSI isolates of *C. albicans*, *C. parapsilosis* and *C. tropicalis*. These species accounted for 78% of all BSI and remained highly susceptible (91–100% S) to fluconazole from 1992 until 2001, irrespective of geographic origin. Rates of fluconazole resistance for these three species were usually ≤3%. In

Table 6. Fluconazole susceptibility of candida bloodstream isolates in each of the nine US Bureau of the Census regions

Species	Region	No. tested	Cumulative percentage inhibited at MIC (μg/mL)[a]										
			0.12	0.25	0.5	1	2	4	8	16	32	64	128
C. albicans	1	214	9	66	89	96	99	99	99[b]	99	99	99	99
	2	168	19	77	89	94	96	97	97[b]	97	97	97	97
	3	183	21	80	91	95	98	98	98[b]	98	98	98	98
	4	92	20	85	92	96	96	98	98[b]	100			
	5	179	15	74	88	94	97	98	98[b]	99	99	99	99
	6	58	10	85	100	100	100	100	100[b]				
	7	39	23	77	97	100	100	100	100[b]				
	8	376	18	78	89	93	95	95	96[b]	97	97	98	99
	9	694	13	75	92	95	98	98	98[b]	99	99	99	99
C. glabrata	1	81	0	0	0	1	14	22	38[b]	79	93	95	98
	2	40	0	3	5	8	13	35	68[b]	88	95	98	98
	3	57	0	0	2	7	12	35	61[b]	95	95	97	100
	4	19	0	0	0	5	47	74	84[b]	90	95	95	95
	5	99	0	0	0	0	9	34	66[b]	91	92	95	100
	6	17	0	0	0	0	18	29	47[b]	71	77	88	100
	7	31	0	0	0	0	26	52	71[b]	100			
	8	138	0	2	4	6	12	34	60[b]	84	86	88	96
	9	190	0	0	0	2	9	31	54[b]	84	90	93	98
C. parapsilosis	1	81	0	6	42	72	94	98	98[b]	99	99	100	
	2	12	0	17	42	83	100	100	100[b]				
	3	23	0	13	61	83	91	96	100[b]				
	4	22	0	5	64	96	100	100	100[b]				
	5	40	0	8	40	76	90	95	100[b]				
	6	4	0	25	75	100	100	100	100[b]				
	7	18	0	0	50	63	63	75	100[b]				
	8	126	0	14	53	87	99	99	100[b]				
	9	171	0	5	37	72	94	97	97[b]	99	100		
C. tropicalis	1	42	0	12	57	76	88	95	98[b]	98	98	98	98
	2	23	0	13	39	74	100	100	100[b]				
	3	32	0	19	72	91	94	97	97[b]	97	97	97	100
	4	16	0	31	63	88	94	94	94[b]	94	100		
	5	35	3	23	54	77	91	94	97[b]	100			
	6	11	0	0	64	82	100	100	100[b]				
	7	4	0	50	75	100	100	100	100[b]				
	8	64	5	25	61	83	95	98	98[b]	100			
	9	127	1	17	43	77	93	96	97[b]	98	98	98	98
All species	1	439	4	35	57	69	78	81	85[b]	94	97	98	99
	2	261	12	54	66	75	80	85	91[b]	95	96	97	97
	3	302	13	52	69	76	81	85	91[b]	97	97	98	99
	4	162	11	53	68	78	84	89	90[b]	94	98	99	99
	5	376	7	39	53	63	69	76	86[b]	94	96	98	99
	6	94	6	53	72	76	81	83	87[b]	94	95	98	100
	7	83	11	39	54	58	68	78	88[b]	99	99	100	
	8	736	10	45	62	73	78	83	88[b]	94	95	97	99
	9	1230	7	45	62	73	80	85	89[b]	95	97	98	99

[a]Broth microdilution testing according to NCCLS M27-A [42].
[b]Percentage of isolates susceptible to fluconazole at the NCCLS breakpoint of ≤ 8 μg/mL.

contrast, the prevalence of fluconazole resistance among *C. glabrata* BSI isolates was quite variable both over time and among the various countries and regions. Surprisingly, the overall susceptibility of *C. glabrata* BSI isolates changed over time with an increase in susceptibility and a decrease in resistance since 1992 (Table 4). Resistance to fluconazole among *C. glabrata* isolates was generally greatest in the USA and varied by US census region (Table 6). Interestingly, fluconazole resistance was not related to the frequency of *C. glabrata* as a cause of BSI in the USA. The highest rates of

susceptibility and lowest rates of resistance were observed in the region with the highest frequency of *C. glabrata* (region 7, 37.3%) as well as in the region with the lowest frequency of *C. glabrata* (region 4, 11.7%) (Tables 3 and 6).

The data presented herein raise several important issues for further investigation. First, it appears that the forces causing variation in the species of *Candida* causing BSI are more complex than simple drug pressure [20]. Variables such as patient age, underlying disease, location in hospital, and local adherence to infection control policies, as well as antifungal drug pressure, may influence the frequency and rank order of *Candida* species causing BSI [2,6,16,18,20,29,30,44]. The fact that the US region with the highest frequency of *C. glabrata* BSI also had the isolates of *C. glabrata* least resistant to fluconazole speaks directly against simple drug pressure as the major cause of the increased prevalence of *C. glabrata* in that region. Several studies have made the observation that the frequency of *C. glabrata* as an aetiological agent of candidemia increases with increasing patient age [6,29,30,45]. This association certainly may be due to drug pressure or underlying disease but one cannot discount the observations of Lockhart *et al*. [46] who demonstrated increased mucosal colonisation with *C. glabrata* among healthy elderly individuals as evidence of significant change in the mucosal flora with age.

The observation of an increase in fluconazole susceptibility and a decrease in resistance over time among *C. glabrata* BSI is perplexing. The fact that all fluconazole susceptibility testing was performed in a central laboratory by the same individuals using NCCLS reference methods argues against 'MIC creep' as a result of variation in MIC endpoint reading criteria being the cause of this shift. Given the mechanism of fluconazole resistance known to occur in *C. glabrata*, induction of CDR efflux pumps [34], one may hypothesise that changes in drug pressure due to improved fluconazole utilisation practices (higher doses, more focused risk-stratified patient selection) may result in this type of change [32,33,47]. Unfortunately the data to support this hypothesis are not readily available. Baddley *et al*. [48] reported a stable rate of fluconazole resistance of approximately 10% among *C. glabrata* BSI, despite a frequency of isolation ranging from 18% to 31% over a 6-year period. Interestingly, Martins *et al*. [49] reported a trend towards reduced rates of carriage of fluconazole-resistant *C. albicans* between 1995 and 1996 in a cohort of human immunodeficiency virus-infected patients following the introduction of highly active antiretroviral therapy (HAART). The authors suggested that decreased use of antifungal agents in patients treated with effective antiretroviral therapy may have contributed to the decrease in fluconazole-resistant strains colonising and infecting these individuals [49]. Thus, similar observations to those made in the present study have been reported by other investigators for *C. albicans* as well as *C. glabrata*. It may be that changes in the overall ecology of *Candida* species occurred in the past 10 years as a result of changes in overall patterns of use for antifungals. At any rate, these observations are intriguing and will require further study to determine the root causes of this change in susceptibility. Regardless, it appears that the susceptibility of candida BSI isolates, including *C. glabrata*, has been stable at least since 1992.

In summary, we have shown that the species distribution of candida BSI isolates varies considerably from region to region throughout the world. *C. albicans* remains the predominant pathogen in almost all areas and actually appears to be stable or even increasing in frequency since 1992. Other observations include an increase in the frequency of *C. glabrata* and a decrease in the frequency of *C. parapsilosis* as aetiological agents of BSI over time in most geographic regions. Variability in the frequency of *C. albicans* and *C. glabrata* as a cause of BSI is quite pronounced in the different regions of the USA but this does not seem to have a great effect on the activity of fluconazole. Fluconazole remains a highly effective agent against most major candida BSI isolates. The documentation that resistance to fluconazole among *C. glabrata* varies by region in the USA and is not directly related to the frequency of isolation of *C. glabrata* is also of great interest. This observation suggests that the emergence of *C. glabrata* as a BSI pathogen is not entirely related to antifungal drug pressure, although drug pressure most likely plays a role in those regions where a decreased susceptibility to fluconazole among *C. glabrata* BSI isolates has been documented. These observations are generally encouraging relative to the sustained usefulness of fluconazole as a systemically active antifungal agent for the treat-

ment of candida BSI. However, they also make a case for continued surveillance, especially on a regional basis, in order to monitor pathogen frequency and change in fluconazole activity, both overall and by specific pathogen.

ACKNOWLEDGEMENTS

Linda Elliott provided excellent support in the preparation of the manuscript.

The International Fungal Surveillance Program was supported in part by research grants from Bristol-Myers Squibb (SENTRY Program), Pfizer (ARTEMIS Program) and Schering Plough (Global Surveillance Program).

We express our appreciation to all International Fungal Surveillance Program participants. Participants contributing to the study included: Christiana Care Health Services, Wilmington, DE (L. Steele-Moore); Clarion Health Methodist Hospital, Indianapolis, IN (G. Denys); Henry Ford Hospital, Detroit, MI (C. Staley); Summa Health System, Akron, OH (J.R. Dipersio); Good Samaritan Regional Medical Center, Phoenix, AZ (M. Saubolle); Denver General Hospital, Denver, CO (M.L. Wilson); University of New Mexico Hospital, Albuquerque, NM (G.D. Overturf); North-western Memorial Hospital, Chicago, IL (L.R. Peterson); University of Illinois at Chicago, Chicago, IL (P.C. Schreckenberger); University of Iowa Hospitals and Clinics, Iowa City, IA (G.V. Doern); Creighton University, Omaha, NE (S. Cavalieri); Froedtert Memorial Lutheran Hospital-East, Milwaukee, WI (S. Kehl); Boston VAMC, Boston, MA (S. Brecher); Columbia Presbyterian Medical Center, New York, NY (L. Lee); Long Island Jewish Medical Center, New Hyde Park, NY (H. Isenberg); Strong Memorial Hospital, Rochester, NY (D. Hardy); St Jude Medical Center, Fullerton, CA (D.S. Koga); Kaiser Regional Laboratory, Berkeley, CA (J. Fusco); Sacred Heart Medical Center, Spokane, WA (M. Hoffmann); University of Washington Medical Center, Seattle, WA (S. Swanzy); Barnes-Jewish Hospital, St Louis, MO (P.R. Murray); Parkland Health & Hospital System, Dallas, TX (P. Southern); The University of Texas Medical School, Houston, TX (A. Wanger); University of Texas Medical Branch at Galveston, Galveston, TX (B. Reisner); University of Louisville Hospital, Louisville, KY (J. Snyder); Carolinas Medical Center, Charlotte, NC (S. Jenkins); University of Virginia Medical Center, Charlottesville, VA (K. Hazen); University of Alberta Hospital, Edmonton, Alberta, CAN (R. Rennie); Health Sciences Center, Winnipeg, Manitoba, CAN (D. Hoban); Queen Elizabeth II Health Sciences Center, Halifax, Nova Scotia, CAN (R. Davidson); Ottawa General Hospital, Ottawa, Ontario, CAN (B. Toye); Sunnybrook Health Science Center, Toronto, CAN (A. Simor); Hospital for Sick Children, Toronto, CAN (S. Richardson); Royal Victoria Hospital, Montreal, Quebec, CAN (H. Robson); Microbiology Laboratory C.E.M.I.C., Buenos Aires, Argentina (J. Smayvsky); Centro de Estudios en Antimicrobianos, Buenos Aires, Argentina (J.M. Casellas); Lamina LTDA, Rio De Janeiro, Brazil (J.L.M. Sampaio); Unidad De Microbiologia Oriente, Santiago, Chile (V. Prado); Centro Diagnostico, Santiago, Chile (P. Garcia); Corp. Para Investig Biologicas, Medellin, Columbia (J.A. Robledo); Instituto Nacional de la Nutricion, Mexico City, Mexico (J.S. Osornio); Laboratorio Medico Santa Luzia, Florianopolis, Brazil (C. Zoccoli); Federal University of Sao Paulo, Sao Paulo, Brazil (A. Reis); Centro Medico De Caracas, San Bernadino, Caracas (M. Guzman); Pathology Medical Laboratories, San Diego, CA (D.A. Schwab); University of Utah Hospitals and Clinics, Salt Lake City, UT (K. Carroll); Lahey Clinic, Burlington, MA (K. Chapin-Robertson); Geisinger Medical Center, Danville, PA (P. Bourbeau); Mount Sinai Medical Center, Miami Beach, FL (S.E. Sharp); Hospital de Clinicas de Porto Alegre, Porto Alegra, Brazil (A.L. Barth); Hospital Erasem, Brussels, Belgium (M.J. Struelens); Hospital de la Pitie-Salpitriere, Paris, France (V. Jarlier/J. Nguyen); A. Calmette, Lille, France (M. Roussel-Delvallez); National University of Athens Medical School, Athens, Greece (N. Legakis); The Chaim Sheba Medical Center, Tel Hashomer, Israel (N. Keller); University Hospital V. de Macarena, Sevilla, Spain (A. Pascual); Hospital de Bellvitge, Barcelona, Spain (J. Linares); Hospital Ramon y Cajal, Madrid, Spain (R. Canton); University Hospital, Lausanne, Switzerland (F. Prapian/J. Bille); Hacettepe Universitaesi Tip Fakultesi, Ankara, Turkey (D. Gur); Marmara Universitesi Tip Fakultesi, Istanbul, Turkey (V. Korten/L. Mulazimoglu); Hacettepe Universitesi Tip Kaultesi, Ankara, Turkey (S. Unal/S. Kocagoz); Universita degli Studi di Genova, Genova, Italy (E. Debbia); St Thomas Hospital, London, UK (G. French), Hôpital Edouard Heriot, Lyon, France (J. Etienne); Institute of Microbiology, Rome, Italy (G. Raponi); Mount Sinai Medical Center, New York, New York (I. Rankin); Azienda Policlinico University Catania, Catania, Italy (G. Nicoletti); Policlinico Agostino Germelli, Rome, Italy (G. Fadda); University Hospital, Linkoping, Sweden (H. Hanberger); Epidemiologia Hospitalaria, Mexico City, Mexico (S. Rangel-Fausto); Institut fur Medizinische, Leipzig, Germany (A.C. Rodloff); Beaumont Hospital, Dublin, Ireland (E. Smyth); Institute of Medical and Veterinary Science, Adelaide, Australia; Institute fur Hygiene und Mikrobiologie, Linz, Austria; Royal Perth Hospital, Perth, Australia (K. Christiansen, G. Coombs); Nagasaki University School of Medicine, Nagasaki, Japan (S. Kohno, Y. 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REFERENCES

1. Rees JR, Pinner RW, Hajjeh RA, Brandt ME, Reingold AL. The epidemiologic features of invasive mycotic infections in the San Francisco Bay Area: results of a population-based laboratory active surveillance 1992–93. *Clin Infect Dis* 1998; **27:** 1138–47.
2. Blumberg HM, Jarvis WR, Soucie JM *et al.* and the NEMIS Study Group. Risk factors for candidal blood stream infections in surgical intensive care unit patients: The NEMIS Prospective Multicenter Study. *Clin Infect Dis* 2001; **33:** 177–86.
3. Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. *Clin Infect Dis* 1999; **29:** 239–44.
4. Rangel-Frausto MS, Wiblin T, Blumberg HM *et al.* National Epidemiology of Mycoses Survey (NEMIS): variations in rates of bloodstream infections due to *Candida* species in seven surgical intensive care units. *Clin Infect Dis* 1999; **29:** 253–8.
5. Sandven P. Epidemiology of candidemia. *Rev Iberoam Micol* 2000; **17:** 73–81.
6. Diekema DJ, Messer SA, Brueggemann AB *et al.* Epidemiology of candidemia: Three-year results from the Emerging Infections and the Epidemiology of Iowa Organisms study. *J Clin Microbiol* 2002; **40:** 1298–302.
7. Hajjeh RA The changing epidemiology of candidemia [abstract S-6]. In: *6th ASM Conference on Candida and Candidiasis. Washington DC* : American Society for Microbiology. 2002: 15.
8. Kao AS, Brandt ME, Pruitt WR *et al.* The epidemiology of candidemia in two United States cities: results of a population-based active surveillance. *Clin Infect Dis* 1999; **29:** 1164–70.
9. Lyon GM, Ponce-DeLeon G, Sofaia AN *et al.* Population-based surveillance for Candida bloodstream infections: Trends in incidence of disease and azole resistance [abstract 217]. In: *40th Interscience Conference on Antimicrobial Agents Chemothertherapy* Washington, DC: American Society for Microbiology, 2000.
10. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Hospital acquired candidemia: attributable mortality and excess length of stay. *Arch Intern Med* 1998; **148:** 2642–5.
11. Rex JH, Walsh TJ, Sobel JD *et al.* Practice guidelines for the treatment of candidiasis. *Clin Infect Dis* 2000; **30:** 662–78.
12. Sheehan DJ, Hitchcock CA, Sibley CM. Current and emerging azole antifungal agents. *Clin Microbiol Rev* 1999; **12:** 40–79.
13. Edwards JE, Bodey GP, Bowden RA *et al.* International conference for the development of a consensus on the management and prevention of severe candidal infections. *Clin Infect Dis* 1997; **25:** 43–59.
14. Meis J, Petrou M, Bille J, Ellis D, Gibbs D. Global Antifungal Surveillance Group. A global evaluation of the susceptibility of *Candida* species to fluconazole by disk diffusion. *Diagn Microbiol Infect Dis* 2000; **36:** 215–23.
15. Rex JH, Rinaldi MG, Pfaller MA. Resistance of *Candida* species to fluconazole. *Antimicrob Agents Chemother* 1995; **39:** 1–8.
16. 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.
17. Boschman CR, Bodnar UR, Tornatore MA *et al.* Thirteen-years evolution of azole resistance in yeast isolates and prevalence of resistant strains carried by cancer patients at large medical center. *Antimicrob Agents Chemother* 1998; **42:** 734–8.
18. Nguyen MH, Peacock JE, 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.
19. Powderly WG. Resistant candidiasis. AIDS. *Res Hum Retroviruses* 1994; **10:** 925–9.
20. Sanglard D, Odds FC. Resistance of *Candida* species to antifungal agents: molecular mechanisms and clinical consequences. *Lancet Infect Dis* 2002; **2:** 73–85.
21. White TC, Marr KA, Bowden RA. Clinical, cellular, and molecular factors that contribute to antifungal drug resistance. *Clin Microbiol Rev* 1998; **11:** 382–402.
22. Pfaller MA, Rhine CJ, Redding SW *et al.* Variations in fluconazole susceptibility and electrophoretic karyotype

among oral isolates of *Candida albicans* from patients with AIDS and oral candidiasis. *J Clin Microbiol* 1994; **32:** 59–64.
23. Redding S, Smith J, Farinacci G *et al.* Resistance of *Candida albicans* to fluconazole during treatment of oropharyngeal candidiasis in a patient with AIDS. documentation by *in vitro* susceptibility testing and DNA subtype analysis. *Clin Infect Dis* 1994; **18:** 240–2.
24. Redding SW, Pfaller MA, Messer SA *et al.* Variations in fluconazole susceptibility and DNA subtyping of multiple *Candida albicans* colonies from patients with AIDS and oral candidiasis suffering from one or more episodes of infection. *J Clin Microbiol* 1997; **35:** 1761–5.
25. Marr KA, White TC, van Burik JAH, Bowden RA. Development of fluconazole resistance in *Candida albicans* causing disseminated infection in a patient undergoing marrow-transplantation. *Clin Infect Dis* 1997; **25:** 908–10.
26. Pfaller MA, Jones RN, Messer SA, Edmond MB, Wenzel RP. National surveillance of nosocomial blood stream infection due to *Candida albicans*: frequency of occurrence and antifungal susceptibility in the SCOPE Program. *Diagn Microbiol Infect Dis* 1998; **31:** 327–32.
27. Pfaller MA, Messer SA, Hollis RJ *et al.* Trends in species distribution and susceptibility to fluconazole among blood stream isolates of *Candida* species in the United States. *Diagn Microbiol Infect Dis* 1999; **33:** 217–22.
28. Chryssanthous E. Trends in antifungal susceptibility among Swedish *Candida* species bloodstream isolates from 1994 to 1998: Comparison of the Etest and the Sensititre Yeast One Colorimetric Antifungal Panel with the NCCLS M-27A reference method. *J Clin Microbiol* 1994; **39:** 4181–3.
29. Pfaller MA, Messer SA, Hollis RJ, Jones RN, Diekema DJ. In vitro activities of ravuconazole and voriconazole compared with those of four approved systemic antifungal agents against 6,970 clinical isolates of *Candida* spp. *Antimicrob Agents Chemother* 2002; **46:** 1723–7.
30. Pfaller MA, Diekema DJ. The role of sentinel surveillance of candidemia: trends in species distribution and antifungal susceptibility. *J Clin Microbiol* 2002; **40:** 3551–7.
31. St. Germain G, Laverdiere M, Pellertier R *et al.* Prevalence and antifungal susceptibility of 442 *Candida* isolates from blood and other normally sterile sites: results of a 2-year, 1996–8, multicenter surveillance study in Quebec. *Can J Clin Microbiol* 2001; **39:** 949–53.
32. Berrouane YF, Herwaldt LA, Pfaller MA. Trends in antifungal use and epidemiology of nosocomial yeast infections in a University hospital. *J Clin Microbiol* 1999; **37:** 531–7.
33. Pfaller MA, Diekema DJ, Jones RN, Sader HS *et al.* The SENTRY Participant Group. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and *in vitro* susceptibilities to fluconazole, ravuconazole, and voriconazole of isolates collected from 1997 through 1999 in the SENTRY Antimicrobial Surveillance Program. *J Clin Microbiol* 2001; **39:** 3254–9.
34. Sanglard D, Ischer F, Calabrese D, Majcherczyk PA, Bille J. The ATP binding cassette transporter gene CgCDR1 from *Candida glabrata* is involved in the resistance of clinical isolates to azole antifungal agents. *Antimicrob Agents Chemother* 1999; **43:** 2753–65.
35. Ellis D, Marriott D, Hajjeh RA, Warnock D, Meyer W, Barton R. Epidemiology: surveillance of fungal infections. *Med Mycol* 2000; **38** (Suppl. 1)**:** 173–82.
36. Pfaller MA. The epidemiology of invasive mycosis-narrowing the gap. *Clin Infect Dis* 1998; **27:** 1148–50.
37. Jones RN. Detection of emerging resistance patterns within longitudinal surveillance systems: data sensitivity and microbial susceptibility. *J Antimicrob Chemother* 2000; **46**(T2)**:** 1–8.
38. Jones RN, Masterton R. Determining the value of antimicrobial surveillance programs. *Diagn Microbiol Infect Dis* 2001; **41:** 171–5.
39. Blignaut E, Pujol C, Lockhart S, Joly S, Soll DR. Ca3 fingerprinting of *Candida albicans* isolates from Human Immunodeficiency Virus-positive and healthy individuals reveals a new clade in South Africa. *J Clin Microbiol* 2002; **40:** 826–36.
40. Pujol C, Pfaller M, Soll DR. Ca3 fingerprinting of *Candida albicans* blood stream isolates from the U.S., Canada, South America, and Europe reveals a 'European' clade. *J Clin Microbiol* 2002; **40:** 2729–40.
41. Warren NG, Hazen KC. *Candida*, *Cryptococcus*, and other yeasts of medical importance. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, eds. *Manual of Clinical Microbiology*, 7th edn. Washington: DC. ASM Press; 1999: 1184–99.
42. National Committee for Clinical Laboratory Standards. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts*. Approved standard. NCCLS publication no. M27-A. Wayne, PA: NCCLS 1997.
43. Rex JH, Pfaller MA, Galgiani JN *et al.* Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of in vitro/in vivo correlation data for fluconazole, itraconazole, and *Candida* infections. *Clin Infect Dis* 1997; **24:** 235–47.
44. Colombo AL, Nucci M, Salomao R. High rate of non-*albicans* candidemia in Brazilian tertiary care hospitals. *Diagn Microbiol Infect Dis* 1999; **34:** 281–6.
45. Kauffman CA. Fungal infections in older adults. *Clin Infect Dis* 2001; **33:** 550–5.
46. Lockhart SR, Joly S, Vargas K, Swails-Wenger J, Enger L, Soll DR. Defenses against oral *Candida* carriage break down in the elderly. *J Dent Res* 1999; **78:** 857–68.
47. Denning DW. Can we prevent azole resistance in fungi? *Lancet*, 1995; **346:** 454–5.
48. Baddley JW, Smith AM, Moser SA, Pappas PG. Trends in frequency and susceptibilities of *Candida glabrata* bloodstream isolates at a University Hospital. *Diagn Microbiol Infect Dis*, 2001; **39:** 199–201.
49. Martins MD, Lozano-Chiu M, Rex JH. Declining rates of oropharyngeal candidiasis and carriage of *Candida albicans* associated with trends toward reduced rates of carriage of fluconazole-resistant *C. albicans*. Clin Infect Dis 1998; 27: 1291–4.