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Epidemiology of Invasive Candidiasis: a Persistent Public Health Problem

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INTRODUCTION

Since the early 1980s, fungi have emerged as major causes of human disease, especially among the immunocompromised and those hospitalized with serious underlying disease (23, 59, 70, 80, 154, 175, 205, 211, 242, 266, 315). A recent study of the epidemiology of sepsis found that the annual number of cases of sepsis caused by fungal organisms in the United States increased by 207% between 1979 and 2000 (150). The morbidity and mortality associated with these infections are substantial (51, 89, 132, 154, 164, 327), and it is clear that fungal diseases have emerged as important public health problems (154, 200, 242, 315). McNeil et al. (154) published an analysis of trends in infectious disease mortality in the United States and found a dramatic increase in multiple-cause mortality due to mycoses, from 1,557 deaths in 1980 to 6,534 deaths in 1997; the majority of these mycoses-related deaths were associated with *Candida*, *Aspergillus*, and *Cryptococcus* sp. infection.

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Predisposing Conditions

Numerous factors have contributed to the increase in fungal infections (Table 1) (266). The most important is an ever-expanding population with immunocompromise due to mucosal or cutaneous barrier disruption, defects in the number and function of neutrophils or in cell-mediated immunity, metabolic dysfunction, and extremes of age (Table 1). Increasing use of broad-spectrum antibiotics, cytotoxic chemotherapies, and transplantation further increases the risk for both common and uncommon opportunistic fungi (175, 211, 302). In addition, as our aging population becomes increasingly mobile, environmental exposures to a variety of endemic fungal pathogens become more common and may further increase the risk of mycotic disease (36).

Spectrum of Pathogens

The list of opportunistic fungi causing serious, life-threatening infection increases every year (13, 80, 175, 200, 211, 227, 242, 302). In addition to *Candida*, *Aspergillus*, and *Cryptococcus* species, the opportunistic fungi include yeasts other than *Candida* species, nondematiaceous or hyaline molds, and the pigmented or dematiaceous fungi (Table 2) (175, 200, 211, 242, 302).

Despite this formidable list of opportunistic fungi, without

TABLE 1. Factors involved in the development of opportunistic mycoses

Factor	Fungal pathogen(s)[a]
Mucosal and cutaneous barrier disruption	*Candida* spp. *Aspergillus* spp.
Neutrophil dysfunction (quantitative or qualitative)	*Candida* spp. *Trichosporon* spp. *Aspergillus* and other molds
Defects in cell-mediated immunity	*Cryptococcus* spp. Endemic mycoses
Metabolic disorders	Zygomycetes *Candida* spp.
Exposures	Endemic mycoses *Aspergillus* and other molds
Extremes of age (<1 and >70 yr)	*Candida* spp.

[a] This list is not all-inclusive.

question the single most important cause of opportunistic mycoses worldwide remains *Candida* (Table 2). By comparison, our understanding of the epidemiology of infections due to other fungal organisms remains rudimentary (242), yet we still have grave deficiencies in the ability to prevent and treat *Candida* infections (89, 92, 189, 274). As a result of several large surveillance efforts, both sentinel (33, 145, 146, 188, 205, 207, 221, 224, 238, 291, 292, 299, 322, 327) and population based (5, 10, 11, 57, 92, 113, 164, 259), we now have a wealth of information regarding invasive candidiasis (IC).

In this article we provide a review of the contemporary epidemiology of IC. We discuss trends in incidence, mortality, species distribution, and antifungal resistance. We also address issues of cost and emerging strategies for the treatment and prevention of this important invasive mycosis.

TABLE 2. Agents of opportunistic mycoses[a]

Organism(s)[b]	No. of cases/ million/yr	Case/fatality ratio (%)
Yeasts		
Candida species	72.8	33.9
C. albicans		
C. glabrata		
C. parapsilosis		
C. tropicalis		
C. krusei		
C. lusitaniae		
C. rugosa		
C. guilliermondii		
C. inconspicua		
C. norvegensis		
Cryptococcus species	65.5	12.7
Other yeasts		
Hyaline molds		
Aspergillus species	12.4	23.3
Zygomycetes	1.7	30.0
Other hyalohyphomycetes	1.2	14.3
Dematiaceous molds	1.0	0
Pneumocystis jiroveci		

[a] Data abstracted from the study of Rees et al. (242).
[b] This list is not all-inclusive.

TABLE 3. Estimated annual number of cases and associated deaths due to nosocomial BSIs with *Candida* species in the United States[a]

Total nosocomial infection rate (%)	Total no. of:			
	Nosocomial infections[b]	Nosocomial BSIs[c]	Nosocomial BSIs due to *Candida*[d]	Deaths due to *Candida* BSIs[e]
2.5	875,000	87,500	7,000	2,800
5	1,750,000	175,000	14,000	5,600
10	3,500,000	350,000	28,000	11,200

[a] Adapted from reference 308 with permission. © 2005 by the Infectious Diseases Society of America. All rights reserved.
[b] Assumes that 35 million patients are hospitalized in the United States each year in critical care settings.
[c] Assumes that 10% of all nosocomial infections are BSIs.
[d] Assumes that 8% of all nosocomial BSIs are due to *Candida* species.
[e] Assumes a 40% mortality rate associated with *Candida* BSIs.

THE BURDEN OF DISEASE: PERSPECTIVES FROM THE NHDS

Candida species are the fourth leading cause of nosocomial bloodstream infection (BSI) in the United States, accounting for 8% to 10% of all BSIs acquired in the hospital (321). Wenzel and colleagues (307, 308) have estimated the number of cases of nosocomial candidemia in the United States (Table 3) by working backward from estimates that (i) 2.5% to 10% of all patients admitted to U.S. hospitals will develop a nosocomial infection, (ii) BSIs represent 10% of all nosocomial infections, and (iii) 8% of nosocomial BSIs are caused by *Candida* species. Given these assumptions, the absolute number of cases of nosocomial candidemia ranges from 7,000 to 28,000 annually (Table 3). If the crude mortality rate of *Candida* BSI is 40%, then 2,800 to 11,200 deaths each year may be associated with nosocomial candidemia. Given that approximately two-thirds of all *Candida* BSIs are nosocomial (92), the total annual burden of candidemia in the United States is approximately 10,500 to 42,000 infections. These estimates are comparable to those obtained from National Hospital Discharge Survey (NHDS) statistics.

The NHDS public-use data files are available on the National Center for Health Statistics (NCHS) website (154, 315). Investigators may query this national database with International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to estimate the incidence and mortality rate for infectious diseases, including IC. Although this approach provides a much more generalizable sample of U.S. hospitals than many other methods of surveillance, it is likely to underestimate both incidence and mortality because of miscoding of IC, use of codes not captured by the analysis, or failure to code the infection at all (79, 154). The NHDS and similar national discharge databases have been used by Wilson et al. (315) to provide estimates of incidence and cost of IC and, for comparison, invasive aspergillosis (IA) for the year 1998. Similarly, Dasbach et al. (51) used NHDS data to estimate the incidence, mortality, and cost of IA for the year 1996. McNeil et al. (154) used NCHS multiple-cause-of-death record tapes to determine national trends in mortality due to invasive mycoses, including a comparison of IC and IA, for the years 1980 through 1996. We have applied this approach to determine the national incidence of IC for the years 1996 through 2003 and mortality rates for the years 1991 through 2003. For

TABLE 4. Incidence of IC and IA in the United States[a]

Parameter	Infection	Incidence rate per yr							
		1996	1997	1998	1999	2000	2001	2002	2003
Incidence rate per 100,000 U.S. population	IC	23	22	22	24	23	22	23	29
	IA	3.4	2.8	2.1	2.4	4.1	3.0	2.6	2.2
Incidence rate per 10,000 hospital discharges	IC	20	19	19	20	20	19	20	24
	IA	3	2	2	2	4	3	2	2

[a] Data are taken from the NHDS, 1996–2003 (http://www.cdc.gov/nchs/).

comparison, we also include incidence and mortality rates for IA over the same time period.

Incidence of Invasive Candidiasis, 1996 to 2003 (NHDS)

The NHDS collects discharge data from a national sample of nonfederal, short-stay hospitals. Weighted data may be used to calculate estimates of the national incidence of a given diagnosis. For our purposes, ICD-9-CM codes 112.4 through 112.9 were used to obtain incidence data for IC, and code 117.3 was used for IA. These were the codes used for IC and IA by Wilson et al. (315) and McNeil et al. (154) and for IA by Dasbach et al. (51). A discharge record was counted if there was a listing of the code in question anywhere on the record. Weighted incidence estimates were calculated with SAS, version 8.1 (SAS Institute, Cary, NC). Incidence rates per 100,000 U.S. population were calculated from population estimates for each year consistent with series P-25, *Current Population Report*, U.S. Bureau of the Census. Incidence rates per 10,000 hospital discharges were calculated with weighted total U.S. discharge estimates from the NHDS.

The national incidence rates for IC, compared with those for IA, for each year from 1996 through 2003 are shown in Table 4. The incidence of IC was remarkably consistent, at 22 to 24 infections per 100,000 population per year (19 to 20 per 10,000 hospital discharges) from 1996 through 2002, with an increase to 29 infections per 100,000 (24 per 10,000 discharges) in 2003. This translates to a national burden of approximately 63,000 infections per year. These numbers are somewhat higher than those estimated by Wenzel and Gennings (308) (Table 3); however, in contrast to the data obtained by Wenzel and Gennings (308), the NHDS data include other types of deeply invasive candidal infections, such as hepatosplenic or other sites of tissue involvement, that may not be associated with candidemia.

The data in Table 4 are directly comparable to those reported by Wilson et al. (315) for the years 1994 and 1996 and by Hajjeh et al. (92) for the Baltimore, MD, metropolitan area (24 per 100,000) in 1998 through 2000. By comparison, population-based studies in the San Francisco, CA, and Atlanta, GA, metropolitan areas and in the states of Iowa and Connecticut report lower annual incidence rates of 6 to 8.7 per 100,000 (discussed in greater detail below) (57, 92, 113). Even when these differences are taken into account, it is clear that the overall burden of disease due to IC is substantial and that the incidence has not decreased over the past decade. This is in contrast to data reported by Trick et al. (292) for nosocomial candidemia in the intensive care unit (ICU) setting during 1989 and 1999. Those investigators used the database of the National Nosocomial Infections Surveillance system to show an overall decline in the frequency of BSIs due to *Candida* among ICU patients in the United States. The decrease was almost entirely due to a decrease in the incidence of *C. albicans* BSI (292). Given the sustained high incidence of IC overall, as seen in both NHDS (Table 4) and population-based studies (Table 5), it may be that IC is shifting from the ICU setting to the general hospital population. Indeed, Hajjeh et al. (92) have shown that in 1998 through 2000, only 36% of *Candida* BSIs occurred in the ICU, whereas 28% were community onset in nature, an increase of almost 10% over that reported in 1992 and 1993 (20% community onset) (113).

Examination of the incidence data for IA helps to put those of IC into perspective. Although there continues to be concern over a perceived increase in both incidence and mortality of IA (43, 44, 51, 85, 132, 149, 154, 194), the overall incidence was almost 10-fold lower than that of IC for the years 1996 through 2003 (Table 4). In fact, the more recent trend in the incidence of IA was from 4.1 infections per 100,000 in 2000 to 2.2 per 100,000 in 2003. This trend is mirrored by the incidence rate per 10,000 hospital discharges (Table 4). The overall burden of disease due to IA was approximately 8,000 infections per year, compared with 63,000 infections per year for IC. These data are similar to those reported by Wilson et al. (315), who found an incidence of IA of 1.9 per 100,000 in 1994 and 3.4 per 100,000 in 1996. Dasbach et al. (51) estimated a disease burden of 10,190 in 1996, with the hospitalization rate for IA ranging from 2.8 per 100,000 population in the northeast to 4.2 per 100,000 in the western United States. Thus, although IA continues to be an important infectious disease, the overall incidence may be decreasing, whereas that of IC has remained steady over the past decade. These findings are

TABLE 5. Estimated incidences of candidemia: population-based studies in Europe, Canada, and the United States

Region	Yr	Location	No. of cases/ 100,000/yr	Reference
Europe	1995–1999	Finland	1.9	234
	1991–1994	Norway	2.0	259
	2001–2003	Norway	3.0	259
	1995–1999	Iceland	4.9	11
	2002–2003	Barcelona	4.9	5
	2003–2004	Denmark	11.0	10
United States	1998–2001	Iowa	6.0	57
	1992–1993	San Francisco, CA	7.1	113
	1992–1993	Atlanta, GA	8.7	113
	1998–2000	Connecticut	7.1	92
	1998–2000	Baltimore, MD	24.0	92
Canada	1999–2004	Calgary	2.8	125

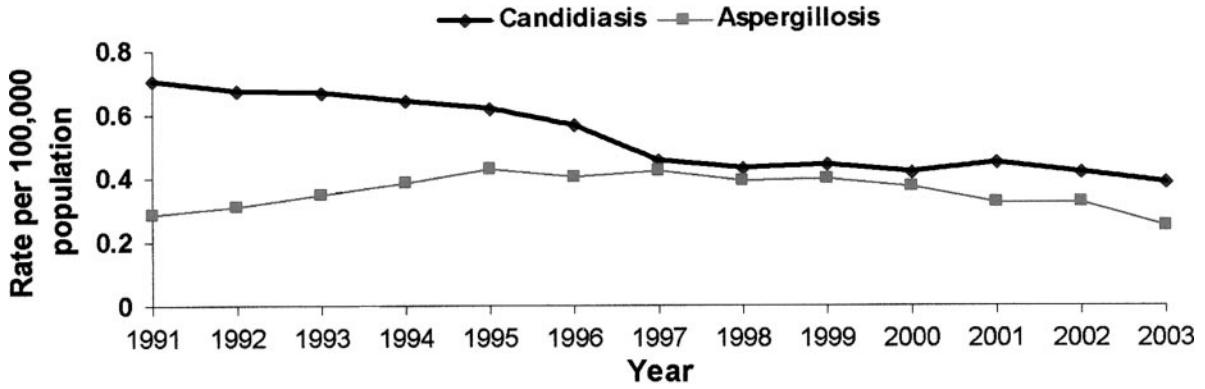

FIG. 1. U.S. crude mortality rates for IC and IA, 1991 to 2003 (NCHS multiple-cause-of-death data from public use files [http://www.cdc.gov/nchs/]).

supported by Morgan et al. (165), who found that IA was an uncommon complication of hematopoietic stem cell transplants (0.5% to 2.9%) and solid organ transplants (0.1% to 2.4%) at 19 U.S. transplant centers from 2001 to 2002.

All-Cause Mortality of IC Compared with That of IA, 1991 to 2003 (NCHS)

As stated by McNeil and colleagues (154), mortality associated with invasive mycoses is best represented by multiple-cause-of-death data, which capture any mention of the mycotic disease on the death certificate. We examined public-use multiple-cause-of-death CD-ROMs provided by the NCHS for the years 1991 through 2003. The NCHS codes mortality using ICD-9 for the years 1991 to 1998 and ICD-10 for 1999 to 2003. We used ICD-9 codes 112.4 through 112.9 to obtain mortality data for IC, and we used code 117.3 for IA. ICD-10 codes were B37.1 and B37.5 through B37.9 for IC and B44.0 through B44.9 for IA. Record axis data were obtained for each of these ICD codes to determine total U.S. mortality. Mortality rates were calculated with the population estimates used to obtain incidence rates above. To control for changes in the age distribution of the population, age-adjusted rates were calculated on the basis of age-specific data, with the age distribution of the 1990 U.S. population used as the standard.

The crude (all-cause) mortality rates associated with IC and IA for the period 1991 through 2003 (deaths per 100,000 population) are shown in Fig. 1. These data are directly comparable to those of McNeil et al. (154) and extend the data reported in that study beyond 1996 to the year 2003. Previously, McNeil et al. (154) demonstrated that mortality rates associated with IC increased steadily from 1980 to a peak in 1989, followed by a gradual decline through 1996. At the same time, they showed an almost exponential increase in the mortality rates associated with IA, with a 357% increase in mortality between 1980 and 1996. Again, the limitations of such data are well known, most notably the lack of validation of the mycotic infection and the failure to clinically diagnose IA and IC, resulting in an underestimation of mortality (154). Regardless, the trends demonstrated by such an analysis should be generalizable, and, at the time the study was published, it appeared that the mortality rate of IA would eventually exceed that of IC.

Figure 1 demonstrates that the mortality associated with IC has remained steady, at approximately 0.4 deaths per 100,000 population per year since 1997, whereas that associated with IA has declined from 0.42 per 100,000 in 1997 to 0.25 per 100,000 in 2003. One can only speculate as to the reasons for these changes. On the one hand, in recent years antifungal therapy options for both IC and IA have been expanded with the introduction of new agents that are effective and less toxic (29, 31, 32, 54, 100, 112, 123, 163, 184, 201, 275, 276, 326). On the other hand, changes in immunosuppressive regimens and improved efforts to document infection may have had a greater impact on the management of IA than on that of IC (4, 43, 44, 59, 80, 85, 164–166, 181, 266, 271, 274, 275, 276). Irrespective of the reasons, both the incidence and mortality associated with IC are not declining, whereas those associated with IA show a steady decrease. The burden of disease due to IC is great, continues to provide significant challenges to the health care system, and warrants continued investigation.

INCIDENCE OF IC FROM POPULATION-BASED SURVEILLANCE

The first population-based estimates of cumulative incidence rates for invasive mycoses came from active laboratory surveillance conducted by the Centers for Disease Control and Prevention in the San Francisco, CA, Bay Area during 1992 and 1993 (242). This study showed a much higher incidence rate for IC (72.8 per million per year) than did previous studies that were based on nonrandom samples of hospital discharge records (77, 200, 243). This active population-based laboratory surveillance design provides information on disease incidence and trends in both the population as a whole and specific risk groups (92, 113, 200, 242). It also captures infections that occur outside the hospital, thus avoiding the bias that may occur in studies that include only selected referral institutions. Analysis of a population-based collection of isolates may provide a more representative estimate of species distribution and the incidence of antifungal resistance within the population analyzed. Active laboratory-based surveillance efforts are more likely to include infections in immunocompromised patients than in others due to the fact that cultures are more likely to be obtained from these patients and, because of the intensity of the infection, are more likely to be positive (200). Conversely, the diagnosis may be hindered by the low sensitivity of culture

and the difficulty of making a diagnosis if cultures are negative. Thus, as with the use of NHDS data and other sentinel surveillance studies, population-based laboratory surveillance has the potential for both overestimation and underestimation of the incidence of mycotic disease. Nevertheless, population-based surveillance remains an excellent means of studying the epidemiology of infectious diseases and has provided extremely useful information, emphasizing the growing threat of invasive mycoses (200).

Coincident with the population-based surveillance conducted in the San Francisco Bay Area, a similarly designed study was conducted to determine the incidence of candidemia in the Atlanta, GA, metropolitan area (113). A detailed description of the epidemiology of candidemia in the San Francisco and Atlanta metropolitan areas was reported by Kao et al. (113) and established an annual average incidence of candidemia of 8 infections per 100,000 population (Table 5). Subsequent population-based studies in Iowa, Connecticut, and the Baltimore, MD, metropolitan area conducted between 1998 and 2001 established a sustained high incidence of candidemia in the United States over a 10-year span. Notably, the incidence of candidemia observed in Baltimore was the same as that found in the NHDS database for the period of 1996 through 2003 (24 infections per 100,000 population) (Table 4).

In addition to population-based surveillance of candidemia in the United States, several similarly designed studies have been conducted in Northern Europe, Spain, and Canada (Table 5). With the exception of Denmark, the incidence of candidemia in Europe and Canada was considerably lower than that reported from the United States, although in each of these studies an increase in incidence was documented over the course of the study. Given the similarities in data collection and analysis across all studies, it is unlikely that the lower rates in Europe and Canada can be explained by differences in study design. Numerous factors likely come into play, including differences in patient demographics and comorbidities, such as age, as well as differences in medical practices, especially the use of long-term vascular catheters and antibacterial and antifungal usage patterns (5, 131, 259). Likewise, the frequency of diagnostic test ordering, especially of blood cultures, and the type of blood culture systems employed may also impact the incidence rates in laboratory-based surveillance (106, 259). Despite the variation in incidence found among the different population-based studies, the rate of IC is far higher than that of any other invasive mycosis (Tables 2 and 4) and is comparable to those of many invasive bacterial diseases (52, 74, 125, 193).

Population-based surveillance also provides the opportunity to accurately define incidence in specific risk groups. In virtually every one of the population-based studies of candidemia, the highest incidence of infection occurred at the extremes of the age spectrum (Table 6). The highest rates of candidemia in infants less than 1 year of age and in adults over the age of 65 have been reported from the two U.S. studies (92, 113). Furthermore, these two studies examined the influence of race on the incidence of candidemia and found that the incidence was at least fourfold higher among blacks in every age group (Table 6). Kao and colleagues (113) examined the incidence of candidemia among neonates (<30 days of age) and found a remarkably high incidence of 466 infections per 100,000 neonates, which again was higher among black neonates (960 per 100,000) than white neonates (238 per 100,000). The discrepancy between rates of infection in black and white infants may be due in part to the elevated incidence of prematurity and low birth weight among black infants (92, 113). These data suggest that certain groups have an incidence of IC so high that serious consideration should be given to prophylactic or preemptive therapy (59, 92, 116, 117, 233, 270).

TABLE 6. Highest incidences of candidemia in the youngest and oldest patient groups: population-based surveillance

Study location	Yr	Incidence (no. of cases/100,000/yr)[a]			Reference
		Total	Patients <1 yr old	Patients ≥65 yr old	
Finland	1995–1999	1.9	9.4	5.2	235
Norway	1991–2003	2.4	10.3	7.0	259
Iceland	1995–1999	4.9	11.3	19.0	11
Spain	2002–2003	4.9	38.8	12.0	5
Canada	1999–2004	2.8	19.0	15.0	125
United States	1992–1993	8 (all)	75 (all)	26 (all)	113
		6 (W)	41 (W)	20 (W)	113
		12 (B)	165 (B)	40 (B)	113
United States	1998–2000	10 (all)	37 (W)	37 (W)	92
			160 (B)	100 (B)	92

[a] W, white patients only; B, black patients only.

Population-based surveillance studies have also documented a high incidence of candidemia among cancer patients (71 per 100,000) and adults with diabetes (28 per 100,000), as well as the near universality of central venous catheters among patients diagnosed with candidemia (5, 92, 113). Regarding the latter observation, it is noteworthy that the formation of biofilms on central venous catheters by *Candida* spp. is associated with nosocomial infections (121, 122). These studies also demonstrate that candidemia is no longer associated exclusively with the ICU, as fewer than 40% of patients in most studies were in an ICU at the time of diagnosis (5, 92, 113). Indeed, 20% to 30% of patients in the U.S. studies were outpatients at the time of diagnosis (92, 113). Interestingly, the proportion of outpatient candidemia in Spain (10.8%) was lower than in the United States (28%), possibly due to a difference in outpatient central venous catheter use and the increasing practice in the United States of the management of various chronic diseases at home rather than in the hospital (5, 92). Taken together, these studies demonstrate that although a significant decrease in annual incidence of candidemia occurred among ICU patients in the 1990s (292), the overall incidence has not decreased and candidemia remains a significant problem worldwide.

GLOBAL TRENDS IN SPECIES DISTRIBUTION AND ANTIFUNGAL SUSCEPTIBILITY AMONG *CANDIDA* ISOLATES FROM IC

Temporal and Geographic Influences on Species Distribution

More than 17 different species of *Candida* have been reported to be etiologic agents of IC in humans (96, 211). Although more than 90% of invasive infections due to *Candida* spp. are attributed to five species—*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*—the list of reported

TABLE 7. Species distribution of *Candida* from cases of invasive candidiasis[a]

Species	% of total no. of cases[b]					
	1997–1998	1999	2000	2001	2002	2003
C. albicans	73.3	69.8	68.1	65.4	61.4	62.3
C. glabrata	11.0	9.7	9.5	11.1	10.7	12.0
C. tropicalis	4.6	5.3	7.2	7.5	7.4	7.5
C. parapsilosis	4.2	4.9	5.6	6.9	6.6	7.3
C. krusei	1.7	2.2	3.2	2.5	2.6	2.7
C. guilliermondii	0.5	0.8	0.8	0.7	1.0	0.8
C. lusitaniae	0.5	0.5	0.5	0.6	0.5	0.6
C. kefyr	0.2	0.4	0.5	0.4	0.4	0.5
C. rugosa	0.03	0.03	0.2	0.7	0.6	0.4
C. famata	0.08	0.2	0.5	0.2	0.4	0.3
C. inconspicua			0.08	0.1	0.2	0.3
C. norvegensis			0.08	0.1	0.07	0.1
C. dubliniensis			0.01	0.08	0.1	0.05
C. lipolytica			0.06	0.06	0.06	0.08
C. zeylanoides			0.03	0.08	0.02	0.04
C. pelliculosa				0.06	0.05	0.04
Candida spp.[c]	3.9	6.0	3.7	3.3	7.9	4.9
Total no. of cases	22,533	20,998	11,698	21,804	24,680	33,002

[a] Data compiled from the ARTEMIS DISK Surveillance Program, 1997 to 2003 (221).
[b] Includes all specimen types and all hospitals from a total of 127 different institutions in 39 countries.
[c] *Candida* species not otherwise identified.

species continues to grow as laboratories are pushed to provide an identification to the species level as an aid in optimizing therapy of candidal infections (Table 7) (189, 211, 253, 274). Recently, we reported the results of the ARTEMIS DISK Antifungal Surveillance Program, in which species identification and the antifungal susceptibility profile were determined for 134,715 consecutive clinical isolates of *Candida* collected from cases of IC (e.g., isolates from blood, normally sterile sites, urine, and genital specimens) in 127 medical centers in 39 countries over a 6.5-year period (1997 through 2003) (Table 7) (221). As can be seen in Table 7, the list of species isolated from clinical specimens continues to grow each year. This is most likely due to the fact that clinical laboratories increasingly are applying both commercially available and classical mycological identification methods for species identification of isolates from clinical specimens (97). However, one cannot discount the possibility that given the increased numbers of immunocompromised individuals worldwide, an ever-increasing number of previously "nonpathogenic" species are truly emerging as opportunistic pathogens (175, 211).

In addition to the increasing number of species reported in surveillance programs such as ARTEMIS (205), temporal changes in species distribution may also be seen (Table 7). Despite the fact that *C. albicans* remained the most common species causing IC worldwide (overall, 66% of all *Candida* spp.), we noted a decreasing trend in the isolation of *C. albicans* over time (Table 7). This decline in the frequency of *C. albicans* is consistent with the findings of Trick et al. (292) in U.S. ICUs. Although neither *C. glabrata* nor *C. krusei* showed a consistent increase or decrease in isolation rate overall, increased rates of isolation of *C. tropicalis* (an increase from 4.6% to 7.5%) and *C. parapsilosis* (an increase from 4.2% to 7.3%) were observed between 1997 and 2003 (Table 7) (221).

Table 7 reveals that the 11 species outside the "top 5" constitute a very small proportion of cases of IC; however, the size and scope of the ARTEMIS Surveillance Program allow one to see that the isolation rates of rare species such as *C. guilliermondii*, *C. kefyr*, *C. rugosa*, and *C. famata* increased between 2- and 10-fold over the course of the study. Overall, however, the rank order of the top eight species was consistent from year to year over the 6.5-year period. We have observed the same temporal trends in species distribution among BSI isolates of *Candida* from 1992 through 2004 (212, 224).

The increase in the number, size, and scope of fungal surveillance programs provides a tremendous amount of data regarding both temporal and geographic variation in the species distribution of *Candida* BSI isolates (Table 8). Although *C. albicans* remains the dominant species causing BSI, the frequency of occurrence varies throughout the world from a low of 37% in Latin America to a high of 70% in Norway.

C. glabrata has undoubtedly emerged as an important opportunistic fungal pathogen in the United States (76, 90, 145, 209, 216, 240, 292). Trick et al. (292) have demonstrated that *C. glabrata* alone among *Candida* species increased in incidence as a cause of BSI in U.S. ICUs between 1989 and 1999, and virtually every U.S.-based survey has shown *C. glabrata* to rank second to *C. albicans* as a cause of BSI, accounting for 20% to 24% of all *Candida* BSIs (Table 8) (57, 92, 113, 145, 146, 183, 188, 205, 207–209, 212, 216, 220, 224, 292). In contrast, *C. glabrata* is much less common as a cause of BSI in most other countries (Table 8), and recent surveys from France (254), Italy (139, 289), Switzerland (147), Finland (234), Iceland (11), Taiwan (33, 34, 107, 108), and Norway (259) indicate that *C. glabrata* has not increased as a cause of IC to the extent in the United States despite an increase in the use of fluconazole in each of those countries. Most notable is the very low frequency of *C. glabrata* as a cause of BSI in Latin America, where only 4% to 7% of *Candida* BSIs are attributed to this species (Table 8).

Although the frequency of isolation of *C. glabrata* from

TABLE 8. Geographic variation in species distribution among BSI isolates of *Candida*

Location	Study period	Reference[a]	No. of isolates	% of total by species						
				C. albicans	*C. glabrata*	*C. parapsilosis*	*C. tropicalis*	*C. krusei*	*C. guilliermondii*	*C. lusitaniae*
United States	1992–1993	113	837	52	12	21	10	4		
United States	1993–1995	205	79	56	15	15	10			
United States	1995–1997	188	1,593	46	20	14	12	2	<1	1
United States	1995–1998	205	934	53	20	10	12	3		
United States	1998–2000	92	935	45	24	13	12	2		
North America	2001–2004	224	2,773	51	22	14	7	2	<1	<1
Canada	1992–1994	322	415	69	8	10	7	1	<1	1
Europe	1992–1994	299	249	49	10	11	11	9		
Latin America	1995–1996	39	145	37	4	25	24	1	2	
Europe	1997–1999	291	2,089	56	14	13	7	2	1	1
Norway	1991–2003	259	1,415	70	13	6	7	2	<1	<1
Taiwan	1994–2000	33	1,095	50	12	14	21	<1		
Spain	2002–2003	5	351	51	9	23	10	4		
Europe	2001–2004	224	2,515	60	10	12	9	5	1	<1
Asia-Pacific	2001–2004	224	1,344	56	10	16	14	2	<1	<1
Latin America	2001–2004	224	1,565	50	7	16	20	2	4	<1
Denmark	2003–2004	10	307	63	20	4	4	3	<1	<1
Spain	2001–2006	49	1,997	47	12	19	10	5	3	1

[a] All studies cited were multicenter surveys.

blood cultures clearly varies across the different studies shown in Table 8, we noted a trend toward decreased isolation in Latin America (7.4% to 4.7% of BSIs), Europe (10.5% to 8.8%), and the Asia-Pacific region (12.1% to 7.2%) between 2002 and 2004 in our global BSI surveillance program (226). The reasons for such dramatic variation in the frequency of *C. glabrata* as a cause of BSI are unclear but may include exposure to azoles, patient age, underlying disease, geographic location, or other, unknown, factors (3, 12, 16, 131, 145, 186, 208, 209, 216, 259). Although most surveillance studies have not specifically addressed the issue of differences among blood culture systems in the isolation of *Candida* species from blood, the isolation of *C. glabrata* may be increased in some blood culture systems (BacT/Alert versus BACTEC 9240) and in some blood culture media (BACTEC Mycosis IC/F versus BACTEC Plus Aerobic/F medium) over that observed in others (106, 158, 259). The extent to which these variables have affected the species distributions reported in the various surveys is unknown.

Several studies have now documented a significant trend toward an increased proportion of BSI due to *C. glabrata* with increasing patient age (Table 9 and Fig. 2) (23, 57, 90, 125, 145, 146, 188, 208, 209, 259). Although the association with fluconazole use and increased isolation of *C. glabrata* is well known (1, 10, 148, 311, 319), the evidence is strongest for cancer centers and less so for individual nonspecialty hospitals (11, 33, 131, 145, 147, 259). Indeed, recent studies by Lin et al. (131) and by Malani et al. (145) did not find exposure to fluconazole to be predictive of *C. glabrata* BSI. Malani et al. (145) found that older adults (age, >60 years) not only had an increased risk of fungemia due to *C. glabrata* but also appeared to have an increased risk of dying from the event. They reported that

TABLE 9. *Candida* species distribution in adults and children as reported by different candidemia surveillance programs

Study population	Surveillance program[a]	Yr	Reference[b]	% of total[c]				
				C. albicans	*C. glabrata*	*C. parapsilosis*	*C. tropicalis*	*C. krusei*
Adults	FDR—Canada	1992–1994	322	71	9	8	7	1
	NEMIS	1993–1995	205	48	24	5	19	0
	MSG	1995–1997	188	45	21	12	12	2
	NNIS	1989–1999	—	59	12	10	11	NA
	CDC	1998–2000	92	44	26	13	13	NA
	SENTRY	1997–2000	205	50	23	12	10	2
Children	CDC	1992–1993	113	53	0	45	0	0
	FDR—Canada	1992–1994	322	56	2	31	6	0
	NEMIS	1993–1995	205	63	6	29	0	0
	MSG	1995–1997	188	49	6	34	8	0
	NNIS	1989–1999	—	54	2	38	4	0
	CDC	1998–2000	92	55	7	19	7	NA
	SENTRY	1997–2000	205	60	3	24	7	0

[a] FDR, Fungal Disease Registry; NEMIS, National Epidemiology of Mycoses Study; MSG, Mycoses Study Group; NNIS, National Nosocomial Infection Surveillance System; CDC, Centers for Disease Control and Prevention.
[b] —, R. A. Hajjeh, presented at the 6th ASM Conference on *Candida* and Candidiasis, Tampa, FL, 13 to 17 January 2002.
[c] NA, not available.

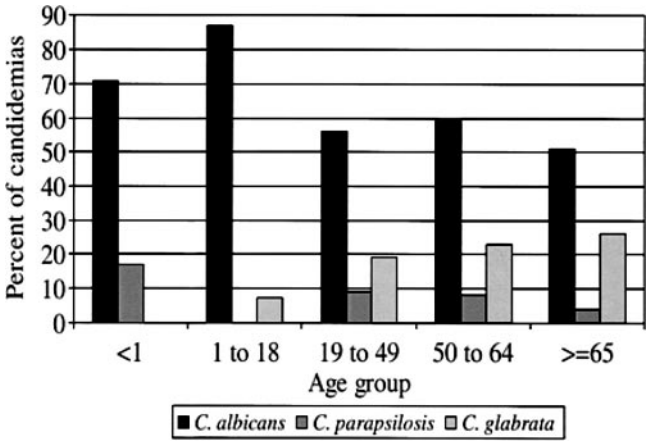

FIG. 2. Percentages of all candidemias due to selected *Candida* species in each group. Data are from the Emerging Infections and the Epidemiology of Iowa Organisms survey, 1998 to 2001 ($P = 0.02$ [for trend of increased frequency of *C. glabrata* with increasing age]). (Adapted from reference 205.)

the most common risk factors for *C. glabrata* BSI were use of broad-spectrum antibiotics, use of central venous catheters, receipt of parenteral nutrition, and stay in an ICU (145). Likewise, Lin et al. (131) found that use of piperacillin-tazobactam and vancomycin was significantly associated with nosocomial BSI due to *C. glabrata* (and *C. krusei*), even after adjusting for clinical risk factors and other antimicrobial uses. Higher rates of oropharyngeal colonization with *C. glabrata* have also been found in older adults and in oncology patients (99, 135, 239–241), although the relationship of this colonization with fungemia is unknown. Taken together, these results appear to contradict the widely held assumption that prior exposure to fluconazole is the single most important predisposing factor for subsequent *C. glabrata* BSI (131, 311). Patient age, exposure to specific antibacterial agents, and severity of underlying disease may be more important than fluconazole exposure in promoting *C. glabrata* candidemia.

In contrast to the situation in the United States, in other countries *C. parapsilosis* and *C. tropicalis*, not *C. glabrata*, are the most common non-*albicans Candida* species causing BSI (Table 8). *C. parapsilosis* is an exogenous pathogen that may be found on skin rather than mucosal surfaces (38, 105, 122, 199, 282, 300, 304). *C. parapsilosis* is notorious for the ability to form biofilms on catheters and other implanted devices (26, 38, 56, 80, 121, 122, 129, 269), for nosocomial spread by hand carriage, and for persistence in the hospital environment (38, 80, 122, 129, 262). It is also well known for causing infections in infants and neonates (Table 9) (130, 138, 255, 262, 264, 300). Recently, it was found that 38% of *C. parapsilosis* BSIs were acquired outside the hospital, consistent with the association of this species with intravascular catheters and parenteral nutrition and with the increase in the management at home of patients with indwelling catheters and various chronic diseases (6, 92, 304). The detection of BSIs with *C. parapsilosis* should raise a "red flag" regarding breaks in catheter care and infection control procedures, as it usually signals the exogenous introduction of the offending pathogen into an already compromised host (6, 129, 199).

The frequency of IC due to *C. parapsilosis* has increased in recent years (Table 7), most notably in Latin America (39, 129). Fortunately, BSI due to this species is associated with a significantly lower mortality rate than are infections due to other species of *Candida* (6, 92, 188). Given the exogenous origin of *C. parapsilosis*, BSIs due to this species should be uniquely preventable by careful attention to good infection control techniques, including hand hygiene and appropriate catheter placement and care (129). Although antifungal prophylaxis with fluconazole has proven effective in preventing candidemia due to *C. parapsilosis* in the neonatal setting (117), a recent example of the emergence of fluconazole resistance in a strain endemic to a Finnish neonatal ICU underscores the importance of good infection control practices, rather than antifungal prophylaxis, in preventing infection with *C. parapsilosis* (262).

C. tropicalis is an important fungal pathogen in patients with neutropenia and those with hematologic malignancies (1, 118, 148, 316). In the United States, fluconazole prophylaxis has decreased the frequency of BSI due to *C. tropicalis*; indeed, the lack of fluconazole prophylaxis was shown to be a predictor of *C. tropicalis* fungemia in patients with hematologic malignancies (1, 118). Despite a decreasing frequency of BSI due to *C. tropicalis* in the United States, the global trend appears to be an increasing frequency of infection with this species (Table 7). Whereas *C. tropicalis* is only the fourth most common species of *Candida* causing BSI in North America (7% of BSIs) (Table 8), it ranks second in Latin America (20%) and is more common than *C. glabrata* in the Asia-Pacific region (14% to 21% versus 10% to 12%, respectively) (Table 8). The risk of *C. tropicalis* infection is increased in the setting of neutropenia and mucositis (53, 301, 317), conditions that are common among patients with hematologic malignancies. As many as 60% to 80% of neutropenic patients who are colonized with *C. tropicalis* eventually develop invasive infection with this species (118, 198, 256). Kontoyiannis et al. (118) have shown that cancer patients with *C. tropicalis* fungemia are more likely to have leukemia, neutropenia, prolonged fungemia, and more days in the ICU than are those with *C. albicans* fungemia.

Like *C. tropicalis*, *C. krusei* is an important pathogen among patients with hematologic malignancies and among blood and marrow transplant recipients (1, 148, 316, 318). *C. krusei* accounts for 2% to 4% of all *Candida* BSIs (Tables 7 to 9), although higher frequencies have been reported for cancer patients in Europe (299) and the United States (1, 148, 318). Although *C. krusei* clearly has emerged among those blood and marrow transplant recipients receiving fluconazole prophylaxis (1, 148, 318), fluconazole exposure alone cannot explain the reported increase in infections caused by this species, since an increase in the prevalence of *C. krusei* predated the use of fluconazole in some institutions (110, 156, 316). Whereas Abi-Said and colleagues (1) found that infections caused by *C. krusei* were strongly associated with fluconazole prophylaxis among neutropenic patients at the M. D. Anderson Cancer Center (Houston, TX), Lin et al. (131) found this not to be the case in the less-specialized tertiary care setting of the University of Chicago Hospitals (Chicago, IL). Lin et al. (131) found that patient exposure to piperacillin-tazobactam and vancomycin was more important than exposure to fluconazole in promoting *C. krusei* BSI. They suggested that these two antibac-

terial agents may promote skin and gastrointestinal tract colonization with *C. krusei* by altering the normal flora and thereby decreasing the colonization resistance of the host (131). Despite the potential for *C. krusei* to emerge as a multidrug-resistant pathogen in the hospital setting, this has not occurred. Longitudinal surveillance dating back to 1992 confirms that this species has consistently accounted for no more than 2% to 4% of *Candida* BSIs worldwide despite widespread use of fluconazole (Tables 7 to 9) (211, 212, 217, 220, 224).

Among the remaining 10 to 12 species of *Candida* known to cause IC (Table 7), there are several that merit discussion either because they have been shown to cause clusters of infection in the hospital setting, because they appear to be increasing in frequency, or because they exhibit decreased susceptibility to one or more antifungal agents and therefore pose a threat of emergence in certain settings (211).

C. guilliermondii and *C. rugosa* are relatively uncommon species of *Candida* that appear to be increasing in frequency as causes of IC (Table 7) (39, 40, 221, 228, 229). These two species are especially common in Latin America, where they each account for 3% to 5% of all candidemias and may be more common than either *C. glabrata* or *C. krusei* (39, 40, 228, 229). Both species have been responsible for clusters of infection in the hospital setting, and both demonstrate decreased susceptibility to fluconazole (39, 40, 65, 151, 211). *C. guilliermondii* is best known as a cause of onychomycosis and superficial cutaneous infections (60, 95); however, Kao et al. (113) found candidemia due to this species to be common among patients with prior cardiovascular or abdominal surgery. Likewise, we have found that the most common clinical specimen to yield *C. guilliermondii* was blood (228). Masala et al. (151) reported a cluster of *C. guilliermondii* catheter-related BSIs among five surgical patients. The infections were successfully treated with catheter removal and administration of fluconazole. The isolates shared a common DNA fingerprint, and nosocomial transmission stopped following reinforcement of infection control measures.

C. rugosa is a rare cause of catheter-related fungemia in most countries (244); however, it has been implicated in clusters of nosocomial fungemia in burn patients in the United States (65) and among critically ill patients in Brazil (40). *C. rugosa* is reported to exhibit decreased susceptibility to both polyenes and fluconazole and may cause catheter-related fungemia in seriously ill patients (175, 244). We have found that *C. rugosa* was recovered most often in cultures of blood and urine obtained from patients hospitalized on medical and surgical in-patient services (229).

C. inconspicua and *C. norvegensis* are both similar phenotypically to *C. krusei* (141, 173, 284). Like *C. krusei*, they exhibit intrinsic resistance to fluconazole (15, 50, 142, 143, 221, 257, 284). *C. inconspicua* has been reported to be a cause of fungemia in human immunodeficiency virus-infected patients and in patients with hematologic malignancies (15, 50). The latter appeared to be due to a common source within the hospital environment, as all affected patients were infected with the same strain, based on DNA restriction profiles. *C. inconspicua* may be especially common in Hungary, where Majoros et al. (143) reported on 57 isolates from 48 patients. Most isolates (70%) were from respiratory tract samples, but wound, blood, and genital isolates were also obtained.

C. norvegensis has been reported from clinical specimens in Norway, The Netherlands, and Japan (284). Although most isolates to date have been from respiratory specimens, Sandven and colleagues (257, 259) have identified this species from blood, urine, and peritoneal fluid.

Trends in Antifungal Susceptibility in Relation to Time, Geographic Location, and Species of *Candida* in Candidemia and IC

Antifungal susceptibility testing in vitro is playing an increasing role in antifungal drug selection, as an aid in drug development studies and as a means of tracking the development of antifungal resistance in epidemiologic studies (4, 202, 253, 274). The Clinical and Laboratory Standards Institute (CLSI) Subcommittee for Antifungal Testing has developed standardized broth microdilution (BMD) (169) and disk diffusion (170) methods for in vitro susceptibility testing of *Candida* spp. These methods are reproducible and accurate and provide clinically useful information that is comparable to that of antibacterial testing (223, 225, 226, 253). Interpretive breakpoints for four systemically active antifungal agents (fluconazole, itraconazole, voriconazole, and flucytosine [5FC]) have been developed by considering data relating the MICs to known resistance mechanisms, the MIC (and zone diameter) distribution profiles, pharmacokinetic (PK) and pharmacodynamic (PD) parameters, and the relationship between in vitro activity (MIC or zone diameter) and clinical outcomes, as determined by the available clinical efficacy studies (225, 226, 250, 251, 253). Although interpretive breakpoints have not been established for posaconazole or the echinocandins, the CLSI Subcommittee has come to a consensus on standardized methods for these agents, and it is expected that interpretive breakpoints will be established in the near future (177, 213, 217).

One of the important by-products of the standardization process has been the ability to conduct active surveillance of resistance to antifungal agents by uniform methods (202, 205, 212, 214, 221, 222). Meaningful large-scale surveys of antifungal susceptibility and resistance conducted over time would not be possible without a standardized microdilution or disk diffusion method for performing the in vitro studies (48, 49, 183, 212, 221, 224). Many such surveys have now been published and include studies of isolates from ICU patients and of nosocomial and community-onset BSIs in several different countries (5, 10, 11, 33, 34, 35, 41, 49, 92, 104, 107, 108, 113, 183, 207, 212, 217, 218, 221, 224, 230, 234, 259, 279, 289, 290, 323). Furthermore, studies of trends in resistance to commonly used antifungal agents such as fluconazole (10, 33, 47, 212, 259) and comparative analyses of licensed and newly introduced antifungal agents (10, 49, 157, 183, 207, 217, 230, 259) have provided large amounts of useful data and have been greatly facilitated by standardized testing methods (see Tables 10 to 18).

Amphotericin B. Detection of resistance to amphotericin B by the CLSI M27-A2 BMD method has been problematic due to the very narrow range of MICs obtained (191, 251, 253). In vitro and in vivo resistance clearly exists (37, 86, 120, 127, 172, 174, 249, 277, 278, 303), and in vitro-in vivo correlations are possible (37, 120, 153, 176); however, the ability to define a clear interpretive MIC breakpoint has proven elusive (191). In

TABLE 10. Is amphotericin B uniformly active against *Candida* species?[a]

Species	No. of isolates tested	MIC (μg/ml)[b]	
		50%	90%
C. albicans	4,195	0.5	1
C. glabrata	949	2	4
C. krusei	234	4	8
C. lusitaniae	103	0.25	1
C. dubliniensis	101	0.25	0.5
C. guilliermondii	102	0.25	1
C. rugosa	13	1	4

[a] Data compiled from references 202, 215, and 216.
[b] Amphotericin B MICs were determined by Etest (204). 50% and 90%, MICs for 50% and 90% of isolates tested, respectively.

general, agar-based methods such as Etest (AB Biodisk, Solna, Sweden) have proven to be the most sensitive and reliable means by which to detect resistance to amphotericin B among *Candida* species (37, 120, 153, 191, 204, 215, 303), although time-kill studies and determination of the minimum fungicidal concentration may also be useful (28, 172, 215). Although interpretive breakpoints for amphotericin B have not been established, isolates of *Candida* for which MICs are >1 μg/ml are unusual and possibly "resistant" or, at the very least, may require high doses of amphotericin B for optimal treatment (189, 253, 274).

Application of the Etest agar-based technology to determine amphotericin B MICs in the context of a broad antifungal surveillance program has identified specific differences in the susceptibilities of the various species of *Candida* to this former "gold standard" antifungal agent (Table 10) (20, 92, 113, 136, 202, 207, 212, 215, 323). Although very little temporal or geographic variation in the susceptibility of *Candida* species to amphotericin B has been observed, it is evident that both *C. glabrata* and *C. krusei* exhibit decreased susceptibility to amphotericin B compared with *C. albicans* (Table 10) (113, 120, 202, 215, 216, 323). Furthermore, amphotericin B exhibits markedly delayed killing kinetics against these two species compared with that against *C. albicans* (28). These findings are reflected in the treatment guidelines for *Candida* infections, wherein higher doses of amphotericin B (≥0.7 mg/kg of body weight/day for *C. glabrata* and 1 mg/kg/day for *C. krusei*) are recommended for these two species (189, 274).

These issues are exemplified in a recent report by Krogh-Madsen and colleagues (120), who describe a series of consecutive isolates of *C. glabrata* with increasing resistance to both amphotericin B and caspofungin recovered from a critically ill patient in an ICU. Amphotericin B MICs determined by Etest ranged from 1.5 μg/ml to 32 μg/ml. An animal model documented therapeutic resistance to amphotericin B for isolates for which the amphotericin B MIC was 6 μg/ml to 8 μg/ml (decreased response) and ≥32 μg/ml (fully resistant). The Etest method was superior to BMD methods in predicting amphotericin B resistance. Reduced susceptibility to amphotericin B was also demonstrated by time-kill studies. This case not only demonstrates the development of amphotericin B resistance in *C. glabrata* but also confirms the Etest as a superior method for detecting such resistance. Of course, the development of resistance to caspofungin in the same strain of *C. glabrata* is of great interest and concern and is discussed below.

Most other species of *Candida* remain susceptible to amphotericin B (191, 215). Resistance is especially rare in *C. albicans*, although Nolte et al. (174) described a strain of ergosterol-deficient *C. albicans* isolated from the blood of two leukemia patients that manifested resistance to both fluconazole and amphotericin B. Recently, Blignaut and colleagues (20) reported that among the five distinct DNA clades of *C. albicans*, the South African clade (clade SA) contained a significantly higher proportion of amphotericin B-resistant (MIC ≥ 2 μg/ml) isolates (16% of 179 isolates) than did the other four clades (5.4% of 167 isolates). This geographic difference in susceptibility to amphotericin B has likely been overlooked, given the paucity of antifungal susceptibility data from South Africa. The SA clade is highly enriched in South Africa (53% of all *C. albicans* isolates), but only 2% of North American isolates and 11% of European isolates belong to this clade (19).

Although notorious for developing clinical resistance to amphotericin B (75, 94, 153, 161, 197, 203), *C. lusitaniae* generally appears to be susceptible to this agent upon initial isolation from blood (Table 10). Thus, resistance to amphotericin B is not necessarily innate in this species but develops secondarily during treatment. *C. lusitaniae* has been shown to exhibit high-frequency phenotypic switching from amphotericin B susceptibility to resistance upon exposure to the drug (160, 324). A recent case report demonstrated the coexistence of two distinct color variants of *C. lusitaniae* upon subculture of positive blood samples onto CHROMagar Candida (Hardy Diagnostics, Santa Maria, CA) (153). One variant (blue colony type) was susceptible to amphotericin B, and one (purple colony type) was resistant. The resistant variant was detected only after intense exposure to amphotericin B therapy, which was clinically unsuccessful. These results emphasize the importance of repeat amphotericin B susceptibility testing for patients with persistent *C. lusitaniae* infection while on amphotericin B therapy (153).

One of the initial case reports describing IC due to *C. guilliermondii* was that of fatal disseminated disease in which the patient succumbed despite amphotericin B therapy (55). The organism was subsequently shown by in vitro testing to be resistant to amphotericin B. Although these findings demonstrate that this species is capable of developing resistance to amphotericin B, it appears to be an important exception (Table 10). Among the 102 incident (i.e., those from the first positive blood culture) BSI isolates tested by Etest in the ARTEMIS Global Surveillance Program (217), only 2 (MICs, 2 μg/ml and 32 μg/ml) appeared to be resistant to amphotericin B (211).

Finally, *C. rugosa* has been isolated in the setting of nystatin prophylaxis (65) and in breakthrough fungemia in patients undergoing treatment with amphotericin B (40). We have found the MIC_{90} for this species (determined by Etest) to be elevated, at 4 μg/ml versus 0.5 μg/ml to 1 μg/ml for *C. albicans* (Table 10) (211).

Thus, despite the perception that amphotericin B and its analogs are broadly active against *Candida* species, evidence is accumulating that suggests less-than-optimal activity against a number of species (189, 274). Fortunately, there are now sev-

TABLE 11. Trends in in vitro resistance to fluconazole among *Candida* spp. determined by CLSI disk diffusion testing over a 6.5-year period (ARTEMIS DISK Surveillance Program, 1997–2003)[a]

Species	Isolates resistant to fluconazole (zone ≤ 14 mm)[b]											
	1997–1998		1999		2000		2001		2002		2003	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
C. *albicans*	16,514	0.8	14,677	0.8	7,961	1.5	14,268	1.0	15,147	1.5	20,576	1.4
C. glabrata	2,475	18.5	2,047	22.8	1,112	14.3	2,431	18.3	2,635	14.7	3,974	16.9
C. tropicalis	1,036	4.2	1,117	3.5	843	3.1	1,634	3.0	1,838	6.6	2,487	5.0
C. parapsilosis	955	2.0	1,028	2.8	650	2.9	1,501	4.2	1,632	3.9	2,406	3.0
C. krusei	372	56.5	459	71.5	376	68.1	544	70.4	639	78.9	884	80.2
C. guilliermondii	111	6.3	168	9.5	88	26.1	163	11.7	239	10.5	260	8.1
C. lusitaniae	115	2.6	99	4.0	62	1.6	122	6.6	131	4.6	211	2.4
C. kefyr	34	0.0	84	4.8	64	3.1	86	2.3	87	5.7	171	2.9
C. rugosa	7	28.6	7	14.3	21	42.9	151	30.5	150	66.0	116	61.2
C. famata	19	47.4	51	9.8	53	13.2	54	14.8	110	10.9	89	11.2
Candida spp.[c]	894	15.5	1,260	7.1	437	10.1	722	9.6	1,953	5.2	1,605	11.4

[a] Isolates from all specimen types and all hospital locations in 127 institutions. Data are from the study of Pfaller et al. (221).
[b] Fluconazole disk diffusion testing performed in accordance with CLSI guideline M44-A (170). *n*, number of isolates.
[c] Species not identified.

eral alternatives to amphotericin B that are both effective and less toxic.

Triazoles. The triazole antifungal agents (i.e., fluconazole, itraconazole, voriconazole, and posaconazole) are safe and effective for the treatment of IC (31, 32, 189, 274). The extended-spectrum triazoles (itraconazole, voriconazole, and posaconazole) exhibit greater potency than fluconazole versus most species of *Candida*, and have promising activity in the treatment of IC (32, 48, 49, 123, 162, 183, 217, 218, 274). All of these agents have the same mechanism of action against *Candida* and, in many instances, are affected by the same resistance mechanisms (24, 32, 81, 225, 226, 260, 274, 294, 312).

The broad use of these agents, especially fluconazole, has given rise to concerns regarding the emergence of resistance to this class of antifungal agents (31, 32, 212, 221, 225, 226, 274). Recent reports suggest that this concern may be warranted for certain species of *Candida* and that close monitoring, including antifungal susceptibility testing, of such infections is prudent (3, 24, 140, 186, 262, 274). As a result, antifungal resistance surveillance with a focus on *Candida* and azole antifungals is now widespread (49, 183, 205, 217, 218, 221, 228, 229). These efforts have been facilitated by the availability of standardized BMD methods, ensuring comparability of results (214, 221, 221) and providing an effective means of tracking trends in resistance to the azoles among the various species of *Candida*.

Fluconazole has been the focus of resistance surveillance efforts since its introduction in the early 1990s (11, 33, 35, 47–49, 92, 98, 107, 108, 113, 207, 212, 217, 221, 259, 279, 290). Among 13,338 BSI isolates of *Candida* (12 species from >200 institutions worldwide) tested by BMD at the University of Iowa between 1992 and 2004, resistance to fluconazole (MIC ≥ 64 μg/ml) was ≤3% for all species, with the exception of *C. glabrata* (9%) and *C. krusei* (40%) (226). These data are highly representative of those published in numerous in vitro studies of *Candida* BSI isolates (11, 33, 35, 47–49, 92, 107, 108, 113, 259, 279, 290).

The longitudinal nature of the ARTEMIS DISK Surveillance Program (1997 to 2003) provides an opportunity to examine trends in fluconazole resistance among clinical isolates of *Candida* (e.g., blood, normally sterile sites, esophageal, genital) with the important advantage of sufficient numbers of isolates of each species, all tested by a single standardized agar disk diffusion method (Table 11) (221). Among the 10 species listed in Table 11, it is notable that fluconazole resistance among isolates of *C. albicans* (0.8% to 1.5%), *C. tropicalis* (3.0% to 6.6%), *C. parapsilosis* (2.0% to 4.2%), *C. lusitaniae* (1.6% to 6.6%), and *C. kefyr* (0.0% to 5.7%) has remained infrequent worldwide (isolates obtained from 127 institutions in 39 countries) over the 6.5-year time span. However, important variations and elevated rates of resistance have been seen among isolates of *C. glabrata* (14.3% to 22.8%), *C. guilliermondii* (6.3% to 26.1%), *C. rugosa* (14.3% to 66.0%), and *C. famata* (9.8% to 47.4%).

Given its prominence as a cause of IC in many settings, *C. glabrata* remains a focus for concern regarding fluconazole resistance (212, 216). Just as the frequency of isolates of *C. glabrata* from patients with IC varies according to the geographic region of origin (Table 8), so does the frequency of resistance to fluconazole (Table 12). In those regions where *C. glabrata* is less common (i.e., Asia-Pacific and Latin America), the isolates are also less resistant to fluconazole (10.6% to 13.2%). Likewise, North America—the region with the highest frequency of *C. glabrata* as a cause of IC—also shows the highest resistance rate (18.0%). Importantly, BSI isolates of *C.*

TABLE 12. Resistance to fluconazole and voriconazole among isolates of *C. glabrata* from four geographic regions, 2001 to 2003[a]

Region	Antifungal agent	No. of isolates tested	% Resistant
Asia-Pacific	Fluconazole	1,859	10.6
	Voriconazole	1,727	4.1
Europe	Fluconazole	4,962	16.5
	Voriconazole	4,801	5.6
Latin America	Fluconazole	940	13.2
	Voriconazole	910	5.4
North America	Fluconazole	1,276	18.0
	Voriconazole	1,278	9.0

[a] Fluconazole and voriconazole disk diffusion testing performed in accordance with CLSI guideline M44-A (170). Data are compiled from the study of Pfaller et al. (221).

TABLE 13. In vitro susceptibilities of rare *Candida* species to fluconazole and voriconazole (ARTEMIS DISK Surveillance Program, 2001–2003)[a]

Species	Fluconazole[b]			Voriconazole		
	No. of isolates tested	% S	% R	No. of isolates tested	% S	% R
C. guilliermondii	662	73	10	633	91	5
C. rugosa	417	39	52	394	61	26
C. inconspicua	187	26	49	186	89	5
C. norvegensis	92	50	38	92	92	1

[a] Data compiled from the study of Pfaller et al. (221).
[b] Abbreviations: S, susceptible; R, resistant.

glabrata from all four monitored geographic regions collected between 2001 and 2004 appear to be progressively more resistant to fluconazole (226).

Cross-resistance between fluconazole and the extended-spectrum triazoles (voriconazole, posaconazole, and itraconazole) is well described among isolates of *C. glabrata* and is associated with increased expression of the genes (Cg*CDR1* and Cg*CDR2*) encoding the *CDR* efflux pumps (24, 211, 216, 217, 218, 221, 225, 226, 260). This can be seen in Table 12, where the rank order of resistance to voriconazole parallels that of fluconazole. This has been manifested clinically where patients with *C. glabrata* fungemia, all with fluconazole exposure, failed treatment with voriconazole (2, 140, 186). The isolates in each instance were resistant to fluconazole (MIC $\geq$ 64 μg/ml) and demonstrated high MICs for voriconazole (MIC = 2 μg/ml to 4 μg/ml), itraconazole (MIC $\geq$ 16 μg/ml), and posaconazole (MIC $>$ 16 μg/ml). Thus, although the triazole antifungal agents may serve as safe and effective treatment options for infections due to *C. glabrata* (189, 274), the susceptibility of this species to fluconazole, or other azoles in the setting of prior azole exposure, is not predictable and requires confirmation by "real-time" antifungal susceptibility testing (4, 14, 91, 140, 186, 189, 274).

Among the less common species of *Candida* known to cause IC, *C. krusei* is well known for its intrinsic resistance to fluconazole (221, 226). In contrast to *C. glabrata*, however, in vitro cross-resistance to voriconazole is distinctly uncommon with *C. krusei* (225) because voriconazole binds much more effectively to the cytochrome P-450 isoenzyme target in *C. krusei* than does fluconazole (81, 274). It also appears that the in vitro activity of voriconazole translates into clinical success in patients infected with *C. krusei* (123, 182, 225).

Although *C. guilliermondii*, *C. rugosa*, *C. inconspicua*, and *C. norvegensis* have been described as species of *Candida* with reduced susceptibility to fluconazole, by and large such statements are based on results from a very small number of isolates (15, 40, 47, 49, 50, 101, 151, 175, 211, 283, 286, 287, 290). Similarly, the susceptibilities of these rare species to voriconazole and other extended-spectrum triazoles are virtually unknown (211). The database provided by the ARTEMIS DISK Antifungal Surveillance Program (221) presents the most extensive experience to date of the susceptibility of these species to fluconazole and voriconazole (Table 13) (228, 229). These data clearly document decreased susceptibility to fluconazole among all four species. Notably, just as the frequency of isolation of *C. rugosa* has increased in recent years (Table 7), its resistance to fluconazole has increased from 30% in 2001 to 61% in 2003 (Table 11). Fortunately, *C. guilliermondii*, *C. inconspicua*, and *C. norvegensis* appear to be susceptible to voriconazole (Table 13). *C. rugosa*, on the other hand, appears to be resistant to voriconazole as well as fluconazole. Resistance to voriconazole among isolates of *C. rugosa* has increased from 3.1% in 2001 to 38.0% in 2002 and 2003 (221, 229). Thus, these four species join the established pathogens—*C. glabrata* and *C. krusei*—as species of *Candida* with reduced susceptibility to the azole antifungal agents and provide further impetus for laboratories to identify isolates of *Candida* to the species level.

Although much of the discussion regarding the extended-spectrum triazoles has focused on their activity against *Aspergillus* and other molds (58), these agents have significantly greater potency than fluconazole against *Candida* spp., including some species such as *C. krusei*, *C. guilliermondii*, *C. inconspicua*, and *C. norvegensis*, with reduced susceptibility to fluconazole (32, 88). There are now several large multicenter surveys that have been conducted with CLSI BMD or very similar (EUCAST [European Committee for Antimicrobial Susceptibility Testing]) BMD methods to provide a direct comparison of the in vitro activities of the extended-spectrum triazoles against BSI isolates of *Candida* (Table 14) (49, 183, 217, 218). The data shown in Table 14 provide a comparison of results obtained from the Global Surveillance Program ($>$100 institutions worldwide) survey conducted by the University of Iowa (217, 218), a 5-year (2001 to 2006) survey of 102 Spanish hospitals (49), and a survey of candidemia in 39 U.S. hospitals (183). These results, encompassing several thousand clinically significant isolates of *Candida* spp., clearly document the excellent, and comparable, potencies of itraconazole, posaconazole, and voriconazole against *Candida* spp. The results were very comparable across all three surveys and generally show MIC_{90}s of $\leq$1.0 μg/ml for all drugs and species, with the exception of *C. glabrata* (Table 14). Although the MIC_{90} for all these triazoles was $>$8.0 μg/ml versus Spanish isolates of *C. pelliculosa*, the MIC_{50}s were all $\leq$1.0 μg/ml and comparable to those observed in the larger sample tested in the Global Surveillance Program. Thus, the high MIC_{90} values in the Spanish survey are likely explained by one or two resistant strains among a total of 10 isolates. Taken together, these data document the good activity of these triazoles against *Candida* spp., with the possible exceptions of *C. glabrata* and *C. rugosa.*

Echinocandins. The echinocandin class of antifungal agents acts by inhibition of the synthesis of 1,3-β-D-glucan in the fungal cell wall. All three available echinocandins—anidulafungin, caspofungin, and micafungin—possess fungicidal activity against most species of *Candida*, including azole-resistant species (29, 54, 152, 157, 201, 296, 326). Caspofungin and anidulafungin have been approved by the U.S. Food and Drug Administration for the treatment of IC, including candidemia, and micafungin has been approved for the treatment of esophageal candidiasis (29, 326). These agents all provide excellent clinical efficacy coupled with low toxicity for the treatment of serious candidal infections.

The optimization of in vitro susceptibility testing of the echinocandins against *Candida* spp. has been difficult (18, 177, 213); however, collaborative studies conducted by the CLSI Antifungal Subcommittee demonstrate that the use of RPMI 1640 broth medium, incubation at 35°C for 24 h, and a MIC

TABLE 14. In vitro activities of itraconazole, posaconazole, and voriconazole against *Candida* species: results from three large multicenter surveys

Species	Antifungal agent	No. and in vitro susceptibility (μg/ml) of isolates by study[a]								
		Pfaller et al. (217, 218)			Cuenca-Estrella et al. (49)			Ostrosky-Zeichner et al. (183)		
		n	MIC_{50}	MIC_{90}	*n*	MIC_{50}	MIC_{90}	*n*	MIC_{50}	MIC_{90}
C. albicans	Itraconazole	3,895	0.06	0.12	940	0.02	0.03	733	0.06	0.5
	Posaconazole	2,359	0.03	0.03	940	0.02	0.02	733	0.03	0.13
	Voriconazole	2,359	0.007	0.015	940	0.02	0.02	733	0.03	0.06
C. glabrata	Itraconazole	1,054	1.0	2.0	244	0.25	1.0	458	1.0	4.0
	Posaconazole	607	1.0	2.0	244	0.25	1.0	458	1.0	2.0
	Voriconazole	607	0.25	1.0	244	0.25	1.0	458	0.25	1.0
C. parapsilosis	Itraconazole	1,028	0.25	0.5	387	0.03	0.06	391	0.13	0.25
	Posaconazole	439	0.12	0.25	387	0.02	0.03	391	0.03	0.13
	Voriconazole	439	0.015	0.12	387	0.02	0.03	391	0.03	0.06
C. tropicalis	Itraconazole	839	0.12	0.25	202	0.02	0.06	307	0.13	1.0
	Posaconazole	319	0.06	0.25	202	0.02	0.06	307	0.06	1.0
	Voriconazole	319	0.06	0.12	202	0.02	0.06	307	0.06	2.0
C. krusei	Itraconazole	206	0.5	1.0	94	0.25	0.25	50	0.5	1.0
	Posaconazole	114	0.5	1.0	94	0.12	0.25	50	0.25	0.5
	Voriconazole	114	0.25	0.5	94	0.25	0.5	50	0.5	1.0
C. lusitaniae	Itraconazole	89	0.12	0.25	21	0.02	0.06	20	0.06	0.25
	Posaconazole	42	0.03	0.12	21	0.02	0.02	20	0.03	0.13
	Voriconazole	42	0.007	0.06	21	0.02	0.02	20	0.03	0.06
C. guilliermondii	Itraconazole	90	0.5	1.0	52	0.25	0.5	9	0.5	
	Posaconazole	45	0.25	0.5	52	0.06	0.12	9	0.06	
	Voriconazole	45	0.06	0.12	52	0.06	0.12	9	0.06	
C. pelliculosa	Itraconazole	28	0.5	1.0	10	0.5	>8.0			
	Posaconazole	16	0.12	0.5	10	1.0	>8.0			
	Voriconazole	16	0.03	0.25	10	0.25	>8.0			

[a] Susceptibility testing performed by either CLSI or EUCAST recommended methods. *n*, number of isolates.

endpoint criterion of prominent reduction in growth (MIC-2, or ≥50% inhibition relative to control growth) provide reliable and reproducible MIC results with good separation of the "wild-type" MIC distribution from isolates with mutations in the *FKS1* gene, for which reduced susceptibility to echinocandins has been documented (177, 192, 213, 220, 224, 230). Studies employing these testing conditions have now been conducted, providing direct comparison of the in vitro activities of the three available echinocandins against a broad range of *Candida* spp. (Table 15) (183, 213, 220, 224, 230).

As seen in Table 15, the multicenter surveys conducted by Pfaller et al. (213, 220, 224, 230) and by Ostrosky-Zeichner et al. (183) both document the excellent potency and spectrum of all three echinocandins against more than 4,000 BSI isolates of *Candida* spp. Both surveys show that the common species—*C. albicans*, *C. glabrata*, and *C. tropicalis*—are highly susceptible to all three agents, whereas elevated MICs (1 μg/ml to 4 μg/ml) are seen for *C. parapsilosis* and *C. guilliermondii*. The available clinical data indicate that these species respond similarly to treatment with each of these agents (29, 41, 87, 114, 119, 163, 184, 219, 274); however, it should be noted that persistent fungemia with *C. parapsilosis* has been observed in the face of caspofungin therapy (163). In light of these findings, it is also important to know that caspofungin has been shown to lack fungicidal activity against *C. parapsilosis* (and *C. guilliermondii*) (17a).

Given the mechanism of action shared by the echinocandins, it is not surprising that they demonstrate similar spectra and potencies. Indeed, scatterplots of anidulafungin MICs (Fig. 3a) and micafungin MICs (Fig. 3b) versus caspofungin MICs show high levels of correlation ($R = 0.83$), with 92% (anidulafungin) to 97% (micafungin) of all MICs for the two comparisons within ± 2 $\log_2$ dilutions of one another (230).

As the first of the echinocandins to be approved for the treatment of IC, caspofungin has been used extensively for the treatment of all forms of serious candidal infections over the past 4 years (87, 114, 134, 171, 261). Thus far, clinical experience with caspofungin and IC has been good (41, 87, 114, 163, 171). However, recent reports describing the emergence of caspofungin resistance during treatment of esophagitis (102), candidemia (63, 120), and endocarditis (167) raise concerns about the emergence of caspofungin-resistant *Candida* spp. (Table 16). In each of these instances, progressive resistance to azoles and other echinocandins, as well as to caspofungin, was observed (Table 16). Furthermore, an additional report described progressive loss of activity of all three echinocandins following prolonged use of micafungin for treatment of *C. albicans* esophagitis (126). The mechanisms of resistance to caspofungin include (i) specific mutations in the *FKS1* genes (which encode essential components of the glucan

TABLE 15. In vitro activities of anidulafungin, caspofungin, and micafungin: results from two large multicenter surveys

Species	Antifungal agent	No. and in vitro susceptibility (μg/ml) of isolates by study[a]					
		Pfaller et al. (220, 224, 230)[b]			Ostrosky-Zeichner et al. (183)[c]		
		n	MIC_{50}	MIC_{90}	*n*	MIC_{50}	MIC_{90}
C. albicans	Anidulafungin	1,483	0.03	0.12	733	0.03	0.03
	Caspofungin		0.03	0.06		0.5	0.5
	Micafungin		0.015	0.03		0.03	0.03
C. glabrata	Anidulafungin	356	0.06	0.12	458	0.03	0.13
	Caspofungin		0.03	0.06		0.5	1.0
	Micafungin		0.015	0.03		0.03	0.06
C. tropicalis	Anidulafungin	269	0.03	0.06	307	0.03	0.13
	Caspofungin		0.03	0.06		0.5	1.0
	Micafungin		0.03	0.06		0.03	0.06
C. krusei	Anidulafungin	63	0.03	0.06	50	0.06	0.13
	Caspofungin		0.06	0.25		1.0	2.0
	Micafungin		0.06	0.12		0.13	0.25
C. parapsilosis	Anidulafungin	383	2.0	4.0	391	2.0	2.0
	Caspofungin		0.5	1.0		2.0	2.0
	Micafungin		1.0	2.0		1.0	2.0
C. guilliermondii	Anidulafungin	45	1.0	2.0	9	1.0	
	Caspofungin		0.5	1.0		1.0	
	Micafungin		0.5	1.0		0.5	
All *Candida* spp.	Anidulafungin	2,663	0.06	2.0			
	Caspofungin		0.03	0.25			
	Micafungin		0.015	1.0			

[a] *n*, number of isolates.
[b] MICs determined in RPMI broth, with a 24-h incubation and a prominent inhibition endpoint.
[c] MICs determined as described in footnote *a* except for a 48-h incubation.

synthesis enzyme complex) and (ii) overexpression of Sbe2p, a Golgi protein involved in transport of cell wall components (15a, 85a, 115, 124, 192). A third mechanism, drug efflux mediated by either CDR or MDR efflux pumps, has been proposed (11a, 85a, 173a). Among these mechanisms, only the *FKS1* mutations have been implicated in clinical resistance (11a, 15a, 115, 124, 192). Such mutations certainly could account for some of the echinocandin cross-resistance patterns noted in the clinical reports (Table 16). These reports serve to emphasize the importance of longitudinal surveillance for emergence of resistance to echinocandins among invasive *Candida* spp.

Recently, we described the results of a global surveillance in which we examined the temporal and geographic trends in the susceptibility of *Candida* spp. to caspofungin since the drug became clinically available (224). The MIC results for an international collection of 8,197 BSI isolates of *Candida* spp. obtained from 91 medical centers between 2001 and 2004 were compared with a previously defined wild-type MIC distribution (3,322 isolates collected between 1992 and 2000) (Table 17). The caspofungin MIC profile of all 8,197 isolates submitted for testing between 2001 and 2004 was unchanged over the 4-year study period, with >99% of isolates tested in each year inhibited by ≤1 μg/ml (Table 17). This MIC distribution was virtually identical to the wild-type MIC distribution for isolates collected in years prior to the introduction of caspofungin (1992 to 2000) (Table 17). Thus, despite the recent case reports of caspofungin resistance developing during treatment of complicated candidal infections, there is no evidence for a shift in the caspofungin MIC distribution over the most recent 4-year period (224).

Although our results do not show a global shift in caspofungin MICs over time, a recent report from a single U.S. hospital demonstrates that resistance to echinocandins can rapidly evolve and spread within a given setting. Vazquez and colleagues had previously described a patient with prosthetic valve endocarditis due to *C. parapsilosis* in which the infecting strain developed progressive resistance to azoles (i.e., fluconazole and voriconazole) and, following treatment with caspofungin, to caspofungin and to micafungin (167). Subsequently, they have documented an increase in the recovery of multiechinocandin-multiazole-resistant *C. parapsilosis* from patients in the burn unit of their hospital (296a). The development, and subsequent nosocomial expansion, of echinocandin-resistant *C. parapsilosis* is alarming and has important clinical implications. It remains to be seen whether the incidence of infection due to *C. parapsilosis* will increase and whether resistance to echinocandins in this species will become common as this class of antifungal drug is used more broadly.

The clinical importance of MIC data for *Candida* and the echinocandins is debatable (18, 114, 219). Recently, Kartsonis et al. (114) reviewed the relationship between caspofungin MICs for baseline isolates of *Candida* obtained from caspofungin-treated patients with either esophageal candidiasis or

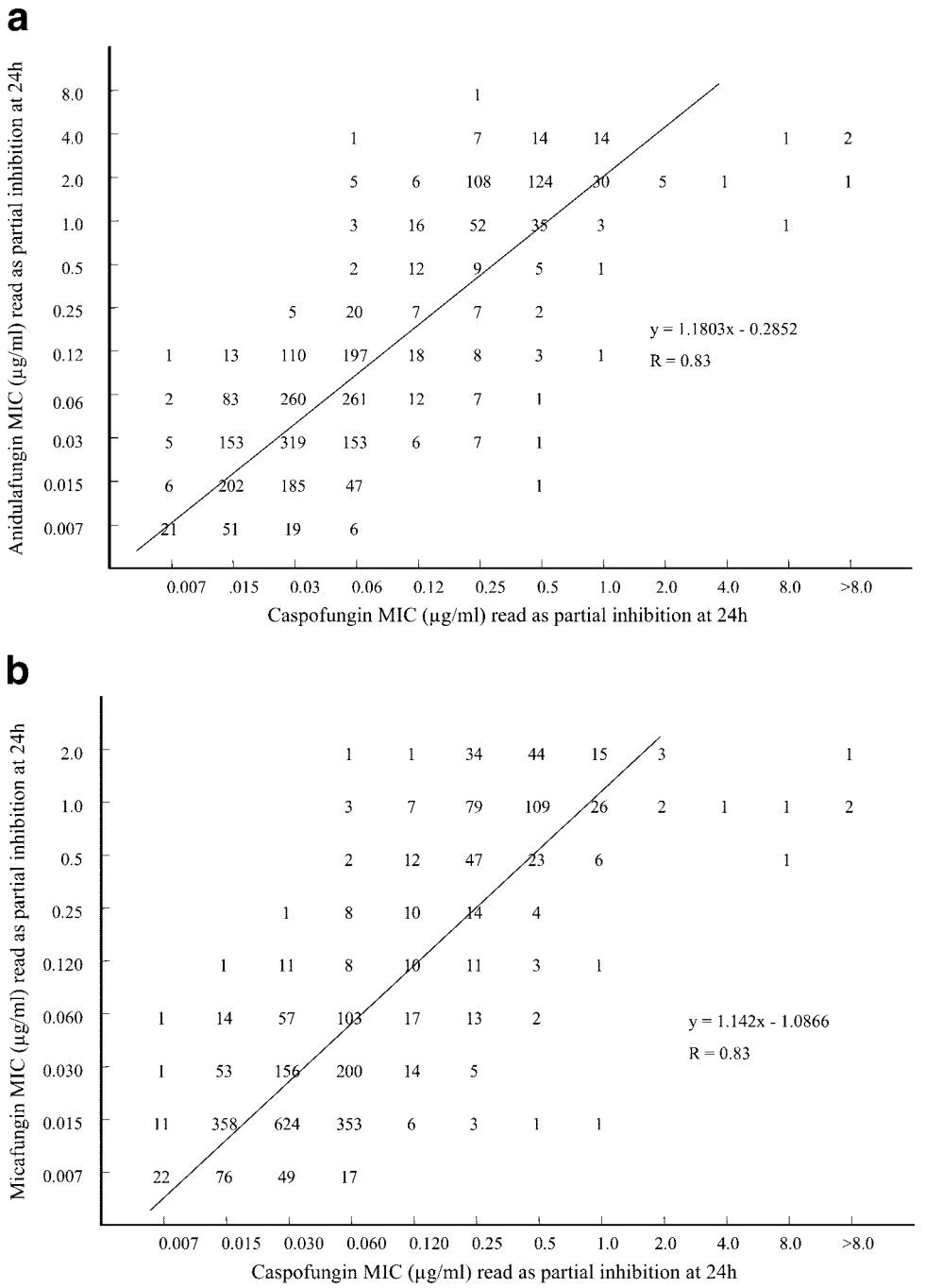

FIG. 3. Scatterplots of anidulafungin (a) and micafungin (b) MICs versus caspofungin MICs for 2,659 isolates of *Candida* spp. MICs were determined for each drug with RPMI 1640 medium, a 24-h incubation, and a partial inhibition (MIC-2) endpoint. (Data in panel b were taken from reference 230.)

IC and clinical outcome of therapy. They concluded that there was no relationship between the in vitro test result and outcome for either infection type. However, the data set included only three isolates from patients treated with caspofungin for which caspofungin MICs were >2 μg/ml (two at 4 μg/ml and one at 8 μg/ml). Thus, the clinical data contain too few patients infected with isolates with reduced susceptibility to caspofungin to permit a firm conclusion regarding the relationship between elevated caspofungin MICs and clinical outcome. The data simply show that clinical failures may occur in the susceptible wild-type population of infecting isolates. These failures are likely due to factors other than the "drug-bug" interaction. Such limitations of clinical trial data have been noted previously (253).

Placing the available echinocandin MIC data in clinical context requires evaluation of (i) the MIC distribution profile

TABLE 16. Clinical and in vitro resistance to echinocandins in patients with candidiasis[a]

Study	Species	Infection type	No. of isolates	Echinocandin MIC range (μg/ml)[b]	Coresistance
Moudgal et al. (167)	*C. parapsilosis*	Endocarditis	6	2–>16*	Caspofungin, micafungin, azoles
Dodgson et al. (63)	*C. glabrata*	Candidemia	15	0.12–>8*	Caspofungin, azoles
Krogh-Madsen et al. (120)	*C. glabrata*	Candidemia	4	0.5–>8*	Caspofungin, amphotericin B, azoles
Hernandez et al. (102)	*C. albicans*	Esophagitis	3	0.25–>64*	Caspofungin, azoles
Laverdiere et al. (126)	*C. albicans*	Esophagitis	4	0.03–2†	Micafungin, caspofungin, azoles

[a] All patients were treated with caspofungin, with the exception of those in the study of Laverdiere et al. (126) (micafungin).
[b] Symbols: *, caspofungin MICs; †, micafungin MICs.

(Table 17), (ii) the known resistance mechanisms and their relation to both MICs and in vivo outcomes, (iii) pertinent PK and PD parameters, and (iv) clinical outcome data (225, 226, 251, 253). With respect to caspofungin and *Candida* spp., we have determined the MIC distribution profile obtained with the optimal BMD method for over 11,000 clinical isolates (Table 17). These results indicate that more than 99% of all clinical isolates of *Candida* spp. are inhibited by ≤1 μg/ml of caspofungin (99.7% at a MIC of ≤2 μg/ml). Similar results are seen for the other two echinocandins (Table 15) (220, 230). In light of this MIC distribution, it is notable that caspofungin MICs (and those of anidulafungin and micafungin) for strains of *Candida* with documented *FKS1* gene mutations (115, 177, 192, 213) and for those published resistant strains (63, 102, 120, 126, 167) were all >2 μg/ml and were usually >8 μg/ml. It is known that such strains respond poorly to echinocandin treatment in animal models and contain a glucan synthesis enzyme complex that is less sensitive to inhibition by the echinocandins than that of wild-type strains, further confirming their status as echinocandin-"resistant" strains (102, 115, 120, 192). Such strains are rarely encountered clinically (<0.3% of 11,519 clinical isolates); however, when observed they appear to exhibit a class-specific resistance profile (Fig. 3) (126, 167). One notable exception is the strain of *C. parapsilosis* described by Moudgal et al. (167), which demonstrated high-level resistance to caspofungin and micafungin (MIC > 8 μg/ml) but not to anidulafungin (MIC = 2 μg/ml). A mechanistic explanation for the lack of resistance to anidulafungin is not apparent. Although these investigators demonstrated overexpression of *MDR1* in the multiechinocandin–multiazole-resistant strains isolated from this and other patients in their institution (296a), this well-known azole resistance mechanism does not explain the observed echinocandin resistance profile (11a, 173a). Regardless, these observations underscore the importance of antifungal susceptibility testing of echinocandins in detecting unusual resistance profiles and raise important questions regarding the development of echinocandin resistance. Further investigation of these issues is warranted.

Pertinent PK data for caspofungin include a peak concentration in serum of approximately 10 μg/ml and a sustained concentration of >1 μg/ml throughout the dosing interval following a loading dose of 70 mg and a daily dosing regimen of 50 mg (61). The area under the concentration-time curve (AUC) is approximately 120 mg · h/liter. Similar PK values are seen with the other echinocandins (61, 326).

PD investigations of caspofungin and *Candida* have been performed, and both in vitro and in vivo models have demonstrated a correlation between drug dose, organism MIC, and outcome (7, 72, 73, 137). Caspofungin (and the other echinocandins) exhibits concentration-dependent killing that is optimized at a peak-to-MIC ratio of ~4:1 and produces a prolonged (>12-h) postantifungal effect (72, 73, 137, 313). Louie et al. (137) have emphasized the importance of the total drug exposure (AUC) for determining caspofungin efficacy in a murine model of systemic candidiasis and have shown that the AUC/MIC ratio is the predictive PD parameter, with a magnitude near 60 predicting efficacy. Others have found that a maximum concentration (C_{max})/MIC ratio of 4:1 or greater was predictive of efficacy for caspofungin (8, 137, 314).

Taken together, the MIC distribution and PK/PD data support a caspofungin MIC of either ≤1 μg/ml or ≤2 μg/ml as predictive of efficacy. A caspofungin MIC of ≤2 μg/ml encompasses 99.7% of all clinical isolates of *Candida* spp., without bisecting any species group (224), and represents a concentration that is easily maintained throughout the dosing interval (61). Given a PD target of an AUC/MIC ratio of 60 (or a

TABLE 17. Comparison of the in vitro susceptibilities of *Candida* isolates collected before (1992 to 2000) and after (2001 to 2004) the clinical introduction of caspofungin[a]

Yr	No. of isolates tested	Cumulative % susceptible at indicated MIC (μg/ml)											
		0.007	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
1992–2000	3,322[b]	23	38	68	84	88	93	98	99	99	99	99	100
2001	1,783	16	35	68	83	88	95	99	99	99	100		
2002	2,239	28	42	68	81	85	91	98	99	99	99	99	100
2003	2,287	7	28	60	78	81	89	98	99	99	99	99	100
2004	1,888	1	14	54	78	82	89	98	99	99	99	99	100
2001–2004	8,197	13	30	62	80	84	91	98	99	99	99	99	100

[a] All isolates were from blood or normally sterile-site infections. All isolates were tested in RPMI 1640 broth with a 24-h incubation period and a prominent reduction endpoint criterion (MIC-2). Data are compiled from reference 224.
[b] Eight of the 11 isolates for which the MICs were ≥2 μg/ml are glucan synthesis mutants.

TABLE 18. Activities of three echinocandin antifungal agents against 315 isolates of fluconazole-resistant *Candida* species[a]

Species (no. of isolates tested)	Antifungal agent	Cumulative % susceptible at MIC (μg/ml)								
		0.007	0.015	0.03	0.06	0.12	0.25	0.5	1	2
C. albicans (41)	Anidulafungin	15	42	66	95	95	95	98	100	
	Caspofungin	2	10	61	95	95	98	98	98	100
	Micafungin	10	76	95	98	98	100			
C. glabrata (110)	Anidulafungin	1	3	36	81	98	100			
	Caspofungin	0	1	59	91	96	100			
	Micafungin	19	93	97	100					
C. krusei (146)	Anidulafungin	1	3	40	82	97	99	100		
	Caspofungin	0	1	1	42	82	97	100		
	Micafungin	1	2	26	93	99	100			
All *Candida* spp. (315)	Anidulafungin	3	9	42	81	94	96	98	99	100
	Caspofungin	1	2	31	66	87	97	99	99	100
	Micafungin	9	44	60	93	96	98	99	100	

[a] MICs were determined in RPMI broth, with a 24-h incubation and a prominent inhibition endpoint. Data are compiled from references 157 and 220.

C_{max}/MIC ratio of ≥4:1), one could predict that standard (70-mg load and 50-mg/day maintenance) caspofungin dosing regimens could successfully be used for treatment of infections due to *Candida* spp. for which MICs are as high as 2 μg/ml. This is supported by the data from clinical trials, as described by Kartsonis et al. (114). Although a MIC predictive of resistance to caspofungin cannot be defined based on data from clinical trials (114, 184, 219), the fact that *FKS1* mutants (115, 192) and isolates of *Candida* spp. from case reports of caspofungin failures (Table 16) all show MICs of 4 μg/ml to >8 μg/ml suggests that the rare isolates for which MICs exceed 2 μg/ml may not respond well to treatment and could be considered "resistant." It is these isolates that are the focus of continued postmarket surveillance for caspofungin and the other echinocandins.

Given the concerns regarding the emergence of fluconazole resistance among isolates of *Candida* spp., it is not surprising that the echinocandins, with their unique mechanism of action, have rapidly become accepted first-line agents for the treatment of serious candidal infections (189, 274). As might be expected from the data shown in Tables 15 and 17, the three echinocandins exhibit excellent activity against both fluconazole-susceptible and -resistant strains of *Candida* (Table 18) (157, 220). In addition to the species shown in Table 18, the echinocandins also are active against fluconazole-resistant strains of *C. rugosa* and *C. inconspicua* (144, 229). Despite this excellent activity against azole-resistant strains, it is notable that in all the case reports describing progressive resistance to echinocandins among strains of *Candida*, the isolates were also highly resistant to the azoles (Table 16). This observation does not necessarily imply that cross-resistance exists between azoles and echinocandins but rather exemplifies the very complex nature of the infections and the fact that efforts to treat the infections with other agents (azoles and polyenes) may have failed prior to treatment with an echinocandin.

5FC. 5FC has been used to treat candidiasis and other invasive mycoses since its introduction in 1968 (285). Although not used as monotherapy, 5FC may be a useful adjunct to other systemically active antifungal agents in the treatment of hematogenous candidiasis (68, 189, 293). Despite a general consensus regarding the clinical efficacy of 5FC when used in combination with other agents (68), clinicians are often hesitant to use this antifungal agent due to concerns about toxicity (78, 297) and either primary or secondary resistance (155, 280, 281, 297). The older literature has stated that primary resistance to 5FC occurred among 10% to 15% of *C. albicans* isolates and was even higher among other species (265, 280). However, more-recent studies using CLSI-based methods strongly refute these statements (17, 46, 104, 206). Studies from Canada (104, 279), the United States (92, 113), Italy (17), and Spain (46) have estimated resistance to 5FC to be 0% to 0.6% for *C. albicans* and 0.6% to 6% for all *Candida* species combined. In a recent study of 8,803 BSI isolates of *Candida* spp. obtained from more than 200 medical centers worldwide (206), we documented a very low level of primary resistance among virtually all *Candida* spp. (<1% to 7%), with the exception of *C. krusei* (28%). This high level of susceptibility among BSI isolates of *Candida* did not vary over time (1992 to 2001) or among the different geographic regions (North America, Latin America, Europe, and Asia-Pacific) represented in the collection (206).

Among the global collection of *C. albicans* isolates discussed above, Pujol et al. (236) have identified three major DNA clades—groups I, II, and III—and two geographically restricted clades: group SA (South African clade) and group E (European clade). Furthermore, it was demonstrated that all of the natural strains of *C. albicans* that were resistant (MIC ≥ 32 μg/ml) to 5FC were members of clade I and that while the 5FC MIC was ≥0.5 μg/ml for 72% of all clade I isolates, the 5FC MIC was ≥0.5 μg/ml for only 2% of all non-group I isolates (237). This clade-specific resistance was subsequently shown to be due to a single nucleotide change in the *FUR1* gene (uracil phosphoribosyltransferase) (62). Strains of *C. albicans* that were heterozygous for the mutation showed decreased susceptibility (MIC, 0.5 μg/ml to 4 μg/ml) to 5FC, and those that were homozygous for the mutation were resistant (MIC > 16 μg/ml) to 5FC. Thus, not all strains or clades of *C. albicans* are equal. These findings suggest that representative strains should be selected from each of the five *C. albicans* clades in future studies of drug resistance or phenotypes of clinical relevance (62).

TABLE 19. Mortality rates, LOS, and costs attributable to candidemia in the United States

Period	Location/patient population	Reference[a]	Mortality (%)	LOS (days)	Cost ($)
1983–1986	Iowa	309	38.0	30.0	NA[b]
1996	Baltimore, MD/ SICU	195	19.0	17.0	21,590
1997–2001	Iowa	89	49.0	10.5	NA
1998–1999	Connecticut	164	19.0	3.4	6,214
1998–2000	Baltimore, MD	164	24.0	12.9	29,094
2000	United States/ pediatrics	327	10.0	21.1	92,266
2000	United States/adults	327	14.5	10.1	39,331
2000	St. Louis, MO	238	35.7	NA	44,051

[a] All studies used a case control or matched-cohort design to estimate attributable (excess) mortality, LOS, and cost.
[b] NA, not available.

TABLE 20. Delay in treatment of *Candida* bloodstream infections is a potential risk factor for hospital mortality[a]

Patient stratum	No. of patients	% Mortality	
		Delay[b]	No delay
AII	157	33.1	11.1
APACHE II ≤ 15	90	23.5	0.0
APACHE II > 15	67	46.0	25.0

[a] Data compiled from the study of Morrell et al. (166).
[b] Delay in administering systemic antifungal therapy of ≥12 h after the first positive blood culture was drawn.

EXCESS MORTALITY, LOS, AND COST OF IC

Candida infections are associated with a high crude mortality of 46% to 75%, reflecting the severe underlying illnesses of the infected patients (59, 67, 70, 195, 321). Given the complex nature of these patients' conditions, it has been difficult to assess the resultant increase in mortality, length of hospital stay (LOS), and costs attributable to the candidal infection (164). In order to better estimate the contribution of the infectious process to mortality, LOS, and costs of care, one must conduct matched-cohort studies where the case patients are carefully matched to control subjects for all variables except for the candidal infections (59, 89, 164, 195, 238, 307, 308, 327). The absolute difference in mortality, LOS, or costs between the case patients and control subjects who were matched for underlying disease is the attributable mortality rate or the excess LOS and cost attributable to the infection (164, 308). These estimates are epidemiologic constructs based on population studies rather than clinical tools (308).

Estimates of the mortality attributable to candidemia and IC have been reported from retrospective matched-cohort studies conducted in single institutions (89, 195, 238, 309) and in the context of population surveillance studies (164, 327) (Table 19). The weight of the evidence provided by these studies suggests that IC is associated with an important attributable mortality (308). Furthermore, these data demonstrate that IC carries no less risk of death during hospitalization today than it did in the 1980s and early 1990s (59). These estimates of attributable mortality are comparable to those for infectious diseases for which large-scale preventative efforts have been made to reduce the incidence and mortality of infection, arguing for increased efforts in candidemia prevention (59, 83, 178, 307, 327).

Attributable mortality estimates derived from retrospective cohort studies have been called into question for attributing all excess deaths among cases to infection (22, 245). Prospective clinical trials estimate mortality attributable to candidemia to be much lower than those observed with a retrospective cohort design (5% to 7% [163, 188, 248] versus 10% to 49% [Table 19]). This may be due in part to the selected nature of the population meeting inclusion criteria for enrollment in clinical trials (89, 327). Furthermore, mortality estimates based on the presence of *Candida* at sterile sites within 48 h of death or at autopsy (163, 188, 248) grossly underestimate attributable mortality by not including deaths among patients who, although they may clear their infection, die of effects related to the physiologic insult sustained during infection (21, 22, 59, 89).

Attributable mortality helps to define the proportion of the crude mortality rate that could be influenced by effective antimicrobial therapy (308). If IC/candidemia creates a negligible attributable mortality (21, 22, 188), then treatment may not be indicated either because the disease is benign and self-limited or because it is simply a harbinger of death due to other serious underlying illness (308). Conversely, those who administer therapy for IC do so with the idea that they are influencing an important contribution to mortality (5, 21, 83, 89, 93, 109, 164, 268, 308).

Treatment of candidemia is often found to be inadequate due to a delay in administration of therapy, treatment with an agent to which the organism is resistant, inadequate dose or duration of treatment, or no treatment at all (5, 21, 83, 89, 93, 109, 164, 166). A recent study at a tertiary care medical center identified failure to administer appropriate antifungal therapy within 12 h of having the first positive blood sample for culture drawn as an independent predictor of hospital mortality (Table 20) (166). Other studies have shown that delays in the initiation of adequate therapy of >24 h (83) and >48 h (21) were independently associated with mortality in candidemic patients. A population-based study conducted in Spain found that removal of vascular catheters, in addition to receipt of at least 5 days of antifungal treatment, was independently associated with a decreased risk for both early and late mortality (5). Likewise, in a recent U.S. population-based study (164), the attributable mortality rate was lower among patients who received adequate (>7 days) treatment for candidemia (11% in Connecticut and 16% in Baltimore and Baltimore County, MD) than among patients who did not receive adequate treatment (31% in Connecticut and 41% in Baltimore and Baltimore County) (Table 21). Thus, reduction of the mortality due to candidemia and IC is dependent on administration of appropriate antifungal therapy (right drug and dose) early in the course of infection and for an adequate duration. Clearly this has important implications for diagnostic testing as well as for prophylactic and empirical treatment strategies.

Several studies have examined the LOS and hospital costs attributable to IC (Table 19). With the exception of the data from the population-based surveillance in Connecticut (164), candidemic patients have been shown to have 10 to 30 more

TABLE 21. Impact of inadequate antifungal therapy on mortality attributable to candidemia, 1998 to 2000[a]

Treatment category	Attributable mortality (%)	
	Connecticut	Baltimore
Overall	19	24
Adequate treatment[b]	11	16
Inadequate treatment[c]	31	41

[a] Data compiled from the study of Morgan et al. (164).
[b] Any systemically active antifungal agent for ≥7 days after first positive blood culture.
[c] Less than 7 days of therapy (30 to 39% of total). Patients who did not survive a minimum of 3 days after a positive blood culture were not included in the analysis.

TABLE 22. Increased hospital costs associated with candidemia[a]

Category	Cost ($)[b]	% of total cost
Total	44,536	100
Length of hospital stay	37,681	84.6
Antifungal therapy	4,710	10.5
Diagnostic procedures	1,513	3.4
Adverse drug reactions	610	1.4

[a] Data compiled from the study of Rentz et al. (246).
[b] In 1997 dollars.

hospital days than control subjects with the same underlying disease and disease severity (Table 19).

Given the prevalence of *Candida* infections and their attributable impact on mortality and LOS, it is not surprising that these infections are associated with substantial health care costs (Table 19) (195). The excess costs attributable to candidemia and IC range from a low of $6,214 per episode in Connecticut to as high as $92,266 among pediatric patients in the United States (164, 327). As expected, the variable most strongly associated with excess costs is the increased LOS (Table 22) (164, 195, 246, 315). The study by Rentz et al. (246) used estimated, not actual, costs and found that 85% of the increase in cost of care for patients with candidemia was due to the excess LOS (Table 22). Likewise, Pelz et al. (195) found that the associations between *Candida* infections and the outcomes of cost and LOS were highly statistically significant and independent of many other clinical variables. Morgan et al. (164) found that inadequately treated patients had a shorter LOS and used fewer resources than adequately treated patients, presumably due to the high mortality rate associated with these patients. Notably, these studies all address costs from the perspective of the hospital and do not account for societal costs, such as lost productivity (195, 327).

Candidemia and other forms of IC carry a significant financial burden (79, 164, 327). Wilson et al. (315) estimated total annual costs of $1.7 billion in 1998 dollars for treatment of candidiasis in the United States. Likewise, Miller et al. (159) suggested that excess medical costs incurred as a result of nosocomial candidemia are approximately four times the previous estimates of $200 million per year (246), approaching $1 billion per year. Given the newer and more expensive treatment options now available, treatment-related costs to the hospital may increase even as attributable mortality decreases (79). Because approximately 95% of the costs of nosocomial infections are borne by hospitals under prospective payment systems, hospitals have a strong incentive to prevent these infections (195, 288, 315). Zaoutis and colleagues (327) have suggested that one life would be saved for every 10 children or every 7 adults in whom candidemia could be prevented. Prevention of candidemia through evidence-based measures of improved hand hygiene, optimal catheter care, and prudent antimicrobial use would reduce both candidemia-related costs and mortality (59, 79, 179). Prophylactic, preemptive, and early empirical antifungal therapy strategies may impact both incidence and mortality due to IC but will require clinical prediction rules that identify subsets of patients who are at particularly high risk for candidemia in order to be effective (59, 252, 273, 327).

RISK FACTORS, TREATMENT, AND PREVENTION STRATEGIES

The burden of IC is tremendous in terms of morbidity, mortality, and cost, and it is clear that we must do more than seek better therapeutic agents if we are to impact this burden (59, 79, 164, 308). Fungal BSIs have been shown to have some of the highest rates of inappropriate initial therapy and hospital mortality among all etiologic agents of BSI examined (93, 109, 166). The most common cause of inappropriate therapy for fungal BSI is the omission of initial empirical therapy (166). Such omission or delay in therapy has been linked directly to mortality (21, 83, 166). Thus, despite an impressive array of new, potent, and nontoxic antifungal agents, we are failing in the management of these infections (59, 166, 185, 238).

Lack of specific clinical findings and slow, insensitive diagnostic testing complicate the early recognition and treatment of IC (4, 166, 168, 185, 295). Most authors recommend the use of clinical risk factors to identify patients who may benefit from prophylactic or early, preemptive, or empirical antifungal therapy in the proper clinical setting (30, 168, 180, 181, 185, 187, 231, 247, 273). Unfortunately, the identified risk factors are all quite common among immunocompromised patients and those critically ill in the ICU. Additional meaningful stratification of identified risk factors will be required to identify those select high-risk patients who would derive maximal benefit from early therapeutic interventions (273).

Risk Factors and Risk Stratification

The risk factors associated with candidemia and IC have been well established and have not changed substantially in the past 2 decades (Table 23) (59, 168, 180, 181, 185, 210, 227, 235, 238, 309). Those determined to be independent risk factors for IC on the basis of multivariate analysis include exposure to broad-spectrum antimicrobial agents, cancer chemotherapy, mucosal colonization by *Candida* spp., indwelling vascular catheter (especially central venous catheter), total parenteral nutrition (TPN), neutropenia, prior surgery (especially gastrointestinal), and renal failure or hemodialysis (Table 23) (23, 59, 128, 166, 168, 181, 185, 187, 231, 235, 273, 310). Prior to 1990, most of the attention was focused on the increased risk of candidemia in patients with malignancies and those with neutropenia (235); however, in recent years the focus has turned to the nonneutropenic patients hospitalized in the ICU, espe-

TABLE 23. Candidemia risk factors for hospitalized patients[a]

Risk factor[b]	Possible role in infection
Antimicrobial agents*	Promote fungal colonization
Number	Provide intravascular access
Duration	
Adrenal corticosteroid	Immunosuppression
Age	Immunosuppression
Chemotherapy*	Immunosuppression
	Mucosal disruption
Malignancy	Immunosuppression
Previous colonization*	Translocation across mucosa
Gastric acid suppression*	Colonization and translocation
Indwelling catheter*	Direct vascular access
Central venous catheter	Contaminated product
Pressure transducer	
TPN*	Direct vascular access
	Hyperglycemia
	Contamination of infusate
Neutropenia ($<500/mm^3$)*	Immunosuppression
Surgery (gastrointestinal)*	Route of infection
	Direct vascular access
Mechanical ventilation	Route of infection
Renal failure/hemodialysis*	Route of infection
	Immunosuppression
Malnutrition	Immunosuppression
Hospital or intensive care unit stay	Exposure to pathogens
	Exposure to additional risk factors
Severity of disease	Immunosuppression
	Invasive procedures

[a] Data compiled from references 59, 168, 180, 181, 185, 210, 227, 235, 238, and 309.
[b] *, independent risk factor.

cially those in the surgical ICU (SICU) (23, 168, 180, 181, 185, 273). Among these patients, the single most important risk factor for IC is prolonged stay in the ICU (185). Although a possible role of each of these risk factors is suggested (Table 23), it is unclear whether they have a causal relationship to the diseases or are just associated markers indicating severity of illness and other predisposing conditions (181).

Most of the risk factors shown in Table 23 represent common interventions or conditions in the hospital and ICU settings and, taken individually, are of little help in determining the risk for IC (168, 181, 273, 305). It is important to realize that the risk for IC is a continuum (227). Among all admissions to the hospital, certain individuals are well known to be at increased risk for acquiring candidemia during hospitalization due to an underlying medical condition: patients with hematologic malignancies or neutropenia, those undergoing gastrointestinal surgery, and both premature infants and patients greater than 70 years of age (1, 9, 23, 70, 92, 148, 188, 255). Within these high-risk groups, specific exposures have been recognized to further increase the risk of IC: the presence of vascular catheters, exposure to broad-spectrum antimicrobial agents, renal failure, mucosal colonization with *Candida* spp., prolonged ICU stay, and receipt of TPN each increase the risk for nosocomial candidemia from 1.7 to 18 times over controls without the specific risk factors or exposures (23, 308, 310). Hospitalization in the ICU setting provides the opportunity for transmission of *Candida* among patients and has been shown to be an additional independent risk factor (23, 70, 181, 255, 308).

When two or more of these risk factors are present, the probability of infection increases exponentially (168, 308). Thus, Wenzel has demonstrated, based on the findings of Wey et al. (310), that in a patient who had received eight different antimicrobials and had *Candida* spp. isolated from a surgical wound and drain effluent, the risk of developing candidemia was 832 times that of a similar patient without antimicrobial therapy or *Candida* colonization (168, 305).

The frequency of these common risk factors for IC renders them less useful when trying to accurately predict which patient in the ICU setting is going to develop IC (181, 273). This has prompted the development of several strategies or risk stratification rules to predict the true risk of disease and to more efficiently identify patients for early diagnostic and therapeutic interventions and thus reduce infection-related deaths (66, 69, 82, 128, 181, 187, 196, 232, 308).

These risk-assessment strategies have been derived either from primary studies to determine risk factors or from clinical trials of prophylaxis (181), and they encompass selection (risk) criteria as simple as a *Candida* colonization index alone (232) or an ICU stay of >3 days (196) to more-complicated formulae, including LOS plus various independent risk factors (66, 82, 128, 187, 308). In each instance, the strategies have been shown to be successful in identifying a subpopulation in which the incidence of IC was increased (10% to 38%) or where the probability of developing IC was increased substantially over the baseline rate or probability for all patients in the ICU. Several of these efforts to develop scoring systems or risk prediction rules have been developed retrospectively and have yet to be validated prospectively in multicenter settings (66, 128, 187, 308). For the most part, these efforts have focused on using data routinely available during the ICU stay to develop rules that would (i) predict significant rates of IC, (ii) capture a substantial proportion of the patients who actually did develop IC, and (iii) be practical for use as selection tools for risk-targeted prevention (prophylaxis) or treatment (preemptive or empirical) strategies (187).

Two recent efforts at risk stratification are worth noting. First, Wenzel and Gennings (308) used four defined risk factors (number of antibiotics, *Candida* colonization, presence of a Hickman catheter, and hemodialysis), plus the assumption of a 1%, 2.5%, or 5% background attack rate for candidemia in the ICU setting, and created a conditional logistic regression model of individual patients' risk of candidemia. They then examined the possibility of using a calculated risk threshold to begin treatment with antifungal agents. They demonstrated that patients with multiple risk factors were at especially increased risk of infection. For example, if a patient has had prior exposure to four antibiotic classes (e.g., cephalosporin, aminoglycoside, glycopeptide, and an antianaerobe agent), the calculated risk to that patient would be 5% to 35% depending on the historical attack rate (1% to 5%) in that ICU. However, with exposure to four antibiotics plus *Candida* colonization, the calculated risks would increase substantially, to 40% to 80% (308). Thus, if validated, this strategy could help test the hypothesis that infections could be prevented if an effective anti-*Candida* agent were administered to high-risk patients at a selected threshold, such as a 33% estimated risk. If subse-

quent intervention trials showed an efficacy of 65% to 100% in preventing infections, one would expect the crude and attributable mortality rates to decrease (308). Furthermore, Wenzel and Gennings showed that by using the known risk factors to identify patients at high risk of candidemia (e.g., 33%) and assuming either a 65% or 100% efficacy of the intervention in preventing candidemia, the necessary number of patients to treat in order to prevent a single death due to candidemia (assuming 25% attributable mortality) would be seven (308), a value similar to that reported by Zaoutis et al. (327).

Leon et al. (128) recently proposed a "*Candida* score" designed to recognize the best candidates for early antifungal therapy in an ICU setting. The score was developed in the context of a large, prospective, multicenter Spanish study in which fungal colonization was assessed weekly along with other potential risk factors. The study population consisted of 1,669 nonneutropenic ICU patients, of which 97 were shown to develop proven candidal infection (candidemia, peritonitis, endophthalmitis). A logistic regression model allowed the authors to identify four independent risk factors: multifocal *Candida* species colonization, surgery upon ICU admission, severe sepsis, and TPN. The *Candida* score was obtained by adding the statistical weight of each risk factor: clinical sepsis (2 points), surgery (1 point), TPN (1 point), and multifocal colonization (1 point). They used receiver operating characteristics to assess the discriminatory power of the *Candida* score and to arrive at a cutoff value of 2.5, providing a sensitivity of 81% and specificity of 74% for identifying patients with current or future IC. Patients with a score of >2.5 were 7.75 times as likely to have proven infection (risk ratio, >7.75; 95% confidence interval [CI], 4.74 to 12.66) as patients with a *Candida* score up to 2.5. These findings provide a framework for the design of new clinical trials concerning early antifungal therapy for nonneutropenic critically ill patients (30).

These various attempts at risk stratification are extremely important in the effort to impact the incidence and mortality rate of IC. Together they show that risk stratification is possible and could contribute to more-accurate selection of patients who could truly benefit from either prophylactic or empirical (or preemptive) antifungal therapy (30).

Prevention and Prophylaxis

Given the substantial excess mortality due to candidemia and the difficulties encountered in administering early and effective antifungal therapy (166, 238), better methods of prevention will decrease candidemia-associated mortality more effectively than will advances in therapy (59, 79, 238). Prevention of nosocomial candidemia is similar to that of many other nosocomial infections and should involve three "low-tech" strategies (59), the first being the implementation of intensive programs to maximize compliance with current hand hygiene recommendations. Such programs are essential; although seemingly simple, compliance with hand washing recommendations among health care providers occurs only 40% of the time in settings where it is indicated (64, 306). Both alcohol and chlorhexidine are effective in killing *Candida* species on the hands of health care workers (25) and will decrease the risk of patients acquiring *Candida* colonization and subsequent infection in the health care setting. Second, strategies to improve adherence to current recommendations for placement and care of central venous catheters (79, 80, 179) are also necessary. An educational program emphasizing essential components of these guidelines successfully reduced catheter-related BSIs due to both bacteria and *Candida* in an SICU (42): catheter-related candidemia was reduced from 12% of all BSIs to 0% in the 18 months following the educational program. Finally, given the importance of antibiotic exposure as a risk factor for candidemia, control of antimicrobial use—especially those with antianaerobic activity (23), as well as piperacillin-tazobactam and vancomycin (131)—is an important component of candidemia prevention. These three strategies—improved hand hygiene, optimal catheter placement and care, and prudent antimicrobial use—should be primary in the approach to prevention of morbidity and mortality resulting from nosocomial candidemia (59, 79). These efforts may also reduce candidemia-related costs by reducing the need to treat central line-related candidemia (79, 80). The remaining preventive strategy, antifungal prophylaxis, must always be considered secondary to the three low-tech approaches and should be applied only when the rate of candidemia remains elevated despite assiduous application of these measures, preferably in a subpopulation within the ICU with a cumulative incidence of IC approaching or exceeding 10% (59).

Antifungal prophylaxis has proven to be effective in decreasing mucosal candidiasis and IC in neutropenic patients (148, 235). Administration of fluconazole (400 mg/day) during neutropenia has proven effective in decreasing infections due to *C. albicans*, *C. tropicalis*, and *C. parapsilosis* (1, 9, 149, 235). This practice has resulted in significant decreases in candidemia and associated mortality despite selecting for fluconazole-resistant strains of *C. glabrata* and *C. krusei* (1, 148). In contrast, the relative benefits and harms and the cost-effectiveness of antifungal prophylaxis in nonneutropenic critically ill patients remain incompletely defined (27, 252, 273), with resultant wide variations in clinical practice (71, 84, 189). Nonetheless, the implementation of targeted antifungal prophylaxis has been shown to be effective in certain ICU settings (23, 27, 133, 298), although the generalizability of these findings has been questioned (59, 273).

Taken individually, the various clinical trials of antifungal prophylaxis in high-risk ICU patients each demonstrate that meaningful prophylaxis is possible (2, 69, 82, 111, 190, 196, 258, 263, 267, 272, 320, 325), although the effect on mortality and the ecological impact in terms of antifungal resistance are less clear. In an effort to provide a systematic synthesis of the benefits and harms of antifungal prophylaxis in the nonneutropenic ICU patient, several groups have conducted meta-analyses of the randomized trials in this area (Table 24) (45, 103, 233, 270, 295). The number of studies included in each analysis varied based on inclusion of trials with agents other than fluconazole, medical versus surgical ICU, or organ transplant; however, all shared a common core of at least four studies and, in the final analysis, the conclusions regarding prophylaxis were quite similar (Table 24).

Despite variability in the rules used to identify high-risk patients for inclusion in the individual trials, the individual and aggregate results all supported a policy of prophylaxis: the use of azole prophylaxis reduced the risk of an invasive form of candidiasis by 50% to 80% (Table 24). The effect on mortality

TABLE 24. Meta-analysis of antifungal prophylaxis in nonneutropenic critically ill and surgical patients: comparison of five recent systematic reviews

Authors (reference)	No. of studies included[a]	Total no. of patients	Patient type	Yr	Antifungal agent(s)[b] (no. of studies)	Effects of prophylaxis on[c]:		
						IFI	Mortality	Resistance
Playford et al. (233)	12	1,606	ICU, surgical	1987–2003	FLC (8), KTC (4)	Decreased by 50%*	Decreased by 25%*	No increase
Vardakas et al. (295)	7	941	SICU	1987–2003	FLC (5), KTC (1), ITC (1)	Decreased by 75%†	Decreased by 25%†	No increase
Cruciani et al. (45)	9	1,226	SICU	1987–2003	FLC (6), KTC (3)	Decreased by 80%†	Decreased by 79%†	NA
Ho et al. (103)	7	814	High-risk surgical	1999–2003	FLC	Decreased by 79%†	No decrease†	NA
Shorr et al. (270)	4	626	SICU	1999–2002	FLC	Decreased by 55%†	No decrease†	No increase

[a] Number of studies included in the meta-analysis.
[b] FLC, fluconazole; KTC, ketoconazole; ITC, itraconazole.
[c] IFI, invasive fungal infection; NA, not assessed; *, refers to IFI due to any fungal pathogen; †, refers to IFI due to *Candida* only. Results for mortality are for mortality due to IFI; results for resistance refer to superinfection or colonization with fungi resistant to the agent used for prophylaxis.

was less clear, although the three larger analyses all showed at least a trend toward a reduction in mortality. Likewise, three of the analyses specifically noted the lack of emergence of azole-resistant *Candida* species or a collective shift in susceptibility patterns; however, it is likely that the size of the data sets is simply too small to detect such a shift (247).

Thus, the picture regarding antifungal prophylaxis in the ICU appears to be coming into better focus (247). The use of antifungal prophylaxis in the ICU population must still remain institution specific and can be justified only if (i) major and concerted efforts have been made to improve hand hygiene, catheter care, and antimicrobial use practices; (ii) the rate of nosocomial candidemia within the ICU remains high despite these efforts; and (iii) a local observational study can define a subpopulation within the ICU with a cumulative incidence of IC approaching or exceeding 10% (59, 308). Playford et al. (233) have used the results from their meta-analysis, coupled with the risk stratification strategies of Rex and Sobel (252) and of Paphitou et al. (187), to demonstrate the potential effects of fluconazole prophylaxis in a range of clinical situations (Table 25). In a subpopulation of ICU patients with an estimated risk of >10%, one would need to treat (prophylax) between 9 (highest-risk category) and 17 (high-risk category) patients to prevent one episode of IC. Given a mortality benefit of approximately 25% for prophylaxis, it was estimated that the number of patients requiring antifungal prophylaxis to prevent one death would range from 83 (95% CI, 49 to 667) among those with a 5% mortality risk to 9 (95% CI, 5 to 67) among those with a 50% risk (233).

These results are very encouraging (247); however, further appropriately powered trials, both to confirm the mortality benefit and to validate the risk selection criteria for identifying specific patient subsets who are likely to derive the greatest benefit, are required (233, 247). Finally, the issues of resistance and the applicability of nonazole antifungal agents (i.e., echinocandins) remain to be addressed. Susceptibility patterns and species identification of infecting isolates should be followed in an organized fashion if routine azole prophylaxis is implemented (3, 140, 247). Clinical trials of prophylaxis with echinocandins are required before these agents can be considered for prophylaxis in the ICU setting.

Thus, prevention and prophylaxis in high-risk patients may reduce the occurrence of IC. However, this approach does not directly address the problem of treatment delays when fungal BSIs do occur (166). At this point it is unknown whether a strategy of targeted prophylaxis would be more useful than one of preemptive or early empirical therapy of infections documented before they produce clinical signs and symptoms or positive cultures (181). Although the latter strategy may be more appealing, it is hindered by the lack of truly robust

TABLE 25. Consideration of risk of invasive fungal infections (IFI) in assessing the impact of fluconazole prophylaxis among critically ill and surgical patients: applicability of meta-analysis results[a]

Estimated risk	Example(s)[b]	Incidence (no. of IFI/100 patients)		No. of IFI avoided/ 100 patients	No. of patients needed to treat to prevent one episode of IFI
		Without prophylaxis	With prophylaxis		
Low (<1%)	Absence of risk factors*	1	0.47	0.53	188
Average (2%)	Unselected intensive care unit population*	2	0.94	1.06	94
High (11%)	One of the following risk factors: diabetes, new-onset hemodialysis, or TPN prior to intensive care unit entry *or* broad-spectrum antibiotics†	11	5.2	5.8	17
Highest (20%)	One of the following risk factors: diabetes, new-onset hemodialysis, or TPN prior to intensive care unit entry *and* broad-spectrum antibiotics*	20	9.4	10.6	9

[a] Data compiled from the study of Playford et al. (233).
[b] Symbols: *, based on reference 252; †, based on reference 187.

surrogate markers or non-culture-based methods for early detection of IC. Such methods are actively being developed but as yet are not widely available (4).

Preemptive and Early Empirical Therapy

"Preemptive" therapy may be defined as early treatment of an infection with the use of clinical, laboratory, or radiological surrogate markers of disease in a high-risk host before clinical signs and symptoms of overt disease develop, whereas "empirical" therapy refers to treatment of high-risk hosts who exhibit signs and symptoms of the disease, even in the absence of positive cultures or other evidence of disease (185). The findings of Morrell et al. (166) showing increased candidemia-related mortality associated with even a minimal delay in administration of effective antifungal therapy would seem to favor a preemptive strategy. Given the imperfect status of surrogate markers for IC, one alternative is to apply risk stratification or a "candidemia score" to choose candidates for preemptive therapy (59). A unique study by Piarroux et al. (231) demonstrated that a targeted preemptive strategy may efficiently prevent acquisition of proven candidiasis in SICU patients. These investigators performed a before/after intervention study, with 2-year prospective and 2-year historical control cohorts. During the prospective period, systematic mycological screening was performed on all patients admitted to the SICU and weekly thereafter until discharge. A corrected colonization index was used to assess the intensity of *Candida* mucosal colonization, and patients with a corrected colonization index of ≥ 0.4 received preemptive therapy with fluconazole (800-mg loading dose followed by 400 mg/day for 2 weeks). The incidence of ICU-acquired proven candidiasis decreased significantly, from 2.2% in the historical control cohort to 0% in the prospective cohort. This study stands as the only example of the feasibility and benefits of using risk stratification, in this case colonization intensity, to direct preemptive antifungal therapy. As such it is encouraging but needs to be confirmed in a prospective multicenter study. Although the authors estimated that the strategy employed was cost-effective and did not result in the emergence of fluconazole resistance, these are both important issues that bear further scrutiny.

There is no literature to address the use of antifungal agents empirically in the febrile, high-risk ICU patient whose microbial cultures are negative. Certainly the ICU patient with a central venous catheter, heavy antimicrobial exposure, and *Candida* colonization at any site has a high risk for candidemia and would likely benefit from early empirical therapy (185, 189). It should be clear that colonization (particularly of many sites) should be regarded as nothing more than a risk factor, not as a disease that requires treatment on its own (185). Again, research in this area is necessary and must focus on identifying these patients by means of risk factor-based clinical prediction rules and determining whether this strategy is more effective than prophylaxis, preemptive therapy, or specific therapy for documented invasive fungal disease (185).

SUMMARY AND CONCLUSIONS

IC is a persistent public health problem. The incidence and mortality rates associated with this infectious disease have remained unchanged for more than a decade despite major advances in the field of antifungal therapy. The excess LOS associated with IC carries with it significant hospital costs, to the extent that annual expenditures for IC have been estimated at ~$1 billion in the United States alone. Epidemiological studies have revealed emerging species that may vary geographically in frequency of isolation. It is also apparent that no class of antifungal agent is immune to the development of resistance. It is now essential that laboratories identify clinical isolates of *Candida* to the species level and consider an orderly program of in vitro susceptibility testing to aid in therapeutic decision making. Mortality attributable to IC remains high largely due to delays in the administration of appropriate antifungal therapy. Considerable effort is now being made toward developing risk stratification strategies to guide antifungal therapy and reduce candidemia-related mortality in an efficient and cost-effective manner. It is unclear at this time which strategy—universal/targeted prophylaxis or preemptive therapy—will be more useful. Fertile areas of research include diagnostics, risk identification, and assessment of management strategies (i.e., prophylaxis, preemptive therapy, or empirical therapy) for IC.

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