Rev Iberoam Micol 2000; 17: 73-81

Epidemiology of candidemia

Per Sandven

Department of Bacteriology, National Institute of Public Health, 0462 Oslo, Norway

The diagnosis of systemic yeast infections is difficult. It is, however, usually agreed that a positive blood culture establishes the diagnosis [1,2]. The isolation of *Candida* from blood is therefore not subject to some of the difficulties involved in defining infection as when yeast is isolated from most other body sites. Blood cultures are, however, often negative in patients with systemic yeast infections [3,4]. Nevertheless, if it is assumed that the proportion of patients with systemic infection having candidemia remains approximately the same over the years, the number of cases with candidemia serves as an important marker of the magnitude of this problem.

Comparison of data between different hospitals or between different time periods in the same hospital is, however, confounded by differences in blood culture methodology, in the manner in which data are collected, in the populations of patients studied etc. Improvements in blood culture methodology may for instance have an important impact. This is exemplified by the finding in many studies some years ago that an increase in the volume of blood cultured increase the recovery of microorganisms [5,6]. Blood culture media has also been improved [7,8]. These changes in methodology have most certainly increased the recovery of all microorganisms including yeasts.

Another important problem is that the occurrence of candidemia is reported in different ways. Usually the total number of candidemia cases for a specific time period is given and sometimes also as a percentage of the total numbers of patients with bacteremia/fungemia. Rates are also reported as the total number of candidemia cases e.g. per 100,000 population, per 10,000 patient days, per 1,000 discharges or per 10,000 admissions to the hospital. All of these reporting methods are quite crude since many factors may influence the results.

With these reservations in mind it is nevertheless interesting to compare the occurrence of candidemia and the distribution of yeast species between hospitals and between countries to provide a broad overview of general trends and changes. This review compares a number of studies from different parts of the world (Tables 1 – 3) in attempt to find an answer to the following questions: a) has the occurrence of candidemia increased? b) Are there differences between countries regarding the occurrence of candidemia? c) What is the species distribution of *Candida* bloodstream isolates in different countries and what is the evidence for a change in the species distribution in recent years?

Has the occurrence of candidemia increased?

A number of studies have identified common risk factors for patients developing a systemic *Candida* infection [9]. Patients that are immunocompromised or immunosuppressed e.g. because of immunosuppressive therapeutic regimens or the use of new and aggressive therapeutic strategies of life support systems are especially at risk [10]. These important changes in medical care have to some extent occurred in all hospitals, but has probably been most marked in intensive care units (ICU), in large tertiary care hospitals and in specialized cancer institutions. Most of the studies on the epidemiology of candidemia have been done in single hospitals and the majority of these hospitals are probably large, specialized hospitals.

The United States and Canada. In an early study on bacteremia and fungemia from the Boston City Hospital covering seven selected years from 1935 – 1972 *Candida* sp. was not detected in the first three years (1935, 1941, 1947). In the next three years (1953, 1961, 1969) the *Candida* rate remained stable at 3.5% – 3.9% of microorganisms isolated from blood culture, but increased to 9% in the last year (1972) of the study [11]. Many institutions reported an increase in the occurrence of candidemia in the mid-1980s. Horn et al. [12] observed that the total number of episodes of fungemia increased by 31% in Memorial Sloan-Kettering Cancer Hospital from the period 1974-1977 to 1978-1982. A study from Harper Hospital showed an increase in the annual incidence of candidemia from 23 episodes (4.6% of the total episodes of sepsis) in 1983 to 48 episodes (6.2% of the total) in 1986 [13]. There also seems to have been a marked increase at the Mayo Clinic from the period 1972-1981 [14] to the period 1984 – 1992 (Table 1) [15]. At the University of Iowa Hospital and Clinics bloodstream infections caused by *Candida* species increased from 2.5% in 1981- 1983 to 7.1% in 1990-1992 [16]. Fraser et al. in a one-year study at Barnes Hospital, St. Louis in 1988-1989 found that candidemia patients represented 0.33% of total patient discharges and this was a 20-fold increase in candidemia compared to the years 1976-1979 [17].

More comprehensive data from the hospitals participating in the National Nosocomial Infections Surveillance system (NNIS) showed a rise in the percentage of all nosocomial bloodstream infections caused by fungi from 5.4% in 1980 to 9.9% in 1990 [18]. During these years the nosocomial fungemia rate increased from 1.0 to 4.9/10,000 discharges. Approximately 180 hospitals in the United States participate in the NNIS system. The hospitals range in size from about 100 beds to more than 1,500 beds [19]. *Candida* was the fourth most common nosocomial bloodstream pathogen among these hospitals [19].

Dirección para correspondencia:
Dr. Per Sandven
Department of Bacteriology,
National Institute of Public Health,
P.O.Box 4404 Torshov,
N-0403 Oslo, Norway.
Tel.: +47 22 04 22 00; Fax: +47 22 04 25 18
E-mail: per.sandven@folkehelsa.no

©2000 Revista Iberoamericana de Micología
Apdo. 699, E-48080 Bilbao (Spain).
1130-1406/99/5.00 Euros

Only one long-term study has been reported from Canada. This study from a 975-bed tertiary care teaching hospital covers a 21-year period from 1976 to 1996 [20]. For the first 15 years the percentage of *Candida* bloodstream isolates was < 2% with the exception of one year when the percentage reached just above 3%. From 1991 a marked increase occurred in that *Candida* accounted for approximately 6% of the total number of isolates in four of these six years and became the fourth most common bloodstream isolate.

Europe. Comparatively few European studies have examined candidemia rates over a prolonged period of time. In one prospective study from a 1,300-bed university hospital in Berlin four 1-year studies on septicemia was done between 1979 and 1989 [21]. A total of 35 patients (3.3% of bloodstream infections) had candidemia in these four years [21]. In five Dutch university hospitals the rate of yeast bloodstream infections doubled from 1987 to 1995, reaching an incidence of 0.76 episodes (candidemia: 0.72 episodes) per 10,000 patient days [22].

A national survey from 1989 to 1998 from Slovakia included 31 microbiological departments serving 71 hospitals [23]. The three first years less than 10 *Candida* episodes were reported each year. During the next four years the number increased to 22-27 episodes per year and in 1996, 1997 and 1998 a further increase to 41, 66 and 65 episodes respectively were noted.

In Norway all fungemia cases have been registered prospectively since 1991. For the years 1991- 96 the candidemia rate was approximately 100 per year for the whole country [24]. This rate has remained the same also for the years 1997 – 99 [P. Sandven, unpublished data]. Prior to 1991 the rate seems to have been somewhat lower. One large university hospital in Norway detected only 18 patients with candidemia in the five-year period 1977-1981 [25]. The average annual number of candidemia episodes at this hospital has increased from 4 in the late seventies to 15 (range 8 – 25) in 1991-99 [P. Sandven, unpublished data]. At another university hospital in Norway, *Candida* accounted for 1% of the microorganisms isolated from blood in the period 1974-1979 and 2.2% (10 episodes per year) in the period 1988-1989 [26]. At this hospital the average number of candidemia episodes has remained at 10 (range 5-16) episodes in 1991 – 1999 [P. Sandven, unpublished data]. The results of the studies from Norway therefore indicate that the candidemia rate has increased from the end of the 1970s to the beginning of 1991. Thereafter the rate seems to have stabilized.

Studies from a Danish university hospital showed stable level of fungemia cases, ranging from 20 to 25 episodes per year between 1984 and 1988, which accounted for <1% of total blood cultures [27]. Thereafter a gradual yearly increase occurred until 57 episodes were recorded in 1994 [28].

India. In a 10-year study (1981-1990) from a 820-bed tertiary care hospital in India a total of 60 patients had candidemia. There was an eleven-fold increase during the last 5 years of the study compared to the first 5 years [29]. In the following six-year period a further marked increase of patients with candidemia was noted at the same hospital from 15 patients in 1991 to 275 patients in 1996 [30].

Taiwan. At the National Taiwan University Hospital a 27-fold increase in bloodstream infections due to *Candida* spp. occurred from 1980 to 1994 and since 1993 *Candida* spp. have become the most common cause of nosocomial bloodstream infections [31].

Unexplained rapid increase in some hospitals. The increase in the number of patients with candidemia has been quite dramatic in some institutions. In a study from one hospital in Houston, Texas the annual candidemia rate was quite steady at approximately 50 cases in 1987-89, but in 1991 and 1992 the annual rate doubled to 107 episodes [32]. At the Nehru Hospital in India the candidemia rate was low (< 20 episodes) in 1981-1991. From 1993 this changed rapidly: 1993 – 112 episodes, 1994 – 139 episodes and 1995 – 275 episodes [29,30]. The increase in candidemia cases at the National Taiwan University Hospital also seems to have taken place quickly [31]. The reasons for such rapid changes in candidemia epidemiology in some institutions are not known.

While it is documented that the candidemia rate has increased in many large, tertiary hospitals, existing documentation is far less convincing as regards smaller, non-specialized hospitals. The NNIS study found an increase in candidemia from the 1980 to 1989 of 75% in small nonteaching hospital and 370% in large nonteaching hospitals [33]. It is, however, probable that the number of nonteaching hospitals that participated in this study was quite limited [19]. In Norway the average annual number of candidemia patients in each county hospital has remained at a steady level of 1 – 5 episodes for the years 1991 – 1999 [P. Sandven, unpublished data]. It is of course possible that this represents an increase from previous years, but in that case the increase is in no way dramatic.

Comparison of candidemia rates

It is important to determine the annual number of patients with bacteremia and fungemia in each hospital to monitor significant changes over the years. Comparisons between hospitals are, however, difficult (Table 1). Most studies report the number of *Candida* episode per year or for a study period. This number is, of course, highly dependent on the size and type of hospital and also on the blood culture practice in each hospital.

In Table 1 the number of candidemia episodes per year per hospital participating in each study has been calculated. In approximately 2/3 of the studies the number of episodes per year was ≤ 20, in 15 studies 21-50, in 2 studies 51-100 and in 5 studies > 100 episodes per year. This is obviously quite a crude way to compare the occurrence of candidemia between hospitals, but it may nevertheless give an indication of the magnitude of the problem. It appears that hospitals in the United States often have more *Candida* cases per year than European hospitals. The majority of the European studies have less than 20 candidemia episodes per year while most of the studies from the United States have more than 20 cases yearly. Five of the seven hospitals reporting a high number of cases (> 50 episodes) are located in the United States. The number of cases reported per year from one cancer institution in the United States [34] is approximately the same as the total number of cases reported per year from cancer patients in 30 tertiary care or university medical centers located in Europe (n = 28) and in the Middle East [35]. These results therefore indicate that the candidemia incidence is higher in the United States than in Europe. It is, however, also possible that this apparent difference only reflects a difference in the size and type of hospitals participating in studies.

In many studies the candidemia rate has been given as a percentage of the total number of patients with bacteremia/fungemia (Table 1). In most of the hospitals in the United States the percentage of candidemia cases is above 5%, while European hospitals usually report 2-3%. In one

Table 1. Number of candidemia episodes reported in studies from various countries.

Year*	Country	Hospital	Candidemia episodes			Reference
			Total no. of episodes/ years	No. per year and per hospital	% of total no. of bloodstream infections	
65-72	USA	1 city/county hospital	72/7	1935,41,47: 0 1953,61,69: 6 – 24 1972: 32	0% 3.5-3.9 % 9%	[71]
72-81	USA	Mayo Clinic	226/10	22.6		[14]
84-92	USA	Mayo Clinic	642/8	80.3	9 %	[15]
72-77	USA	1 hospital	85/4.5	18.9		[72]
74-77	USA	Memorial Sloan-Ketteringr Cancer Cente	129/4	32.3		[69]
78-82	USA	Memorial Sloan-Kettering Cancer Cente	200/4.5	44.4		[12]
75-81	USA	Surgical patients in 1 hospital	63/6.5	9.7		[73]
76-83	USA	3 hospitals	117/7.8	5		[41]
78-79	USA	1 university hospital	71/1	71		[74]
80-89	USA	1 university hospital	232/10	1980-84: 18 1985-89: 30	8.8 % 12.9 %	[75]
81-92	USA	1 university hospital	251/12	1981-83: 5.7 1984-86: 22.7 1987-89: 24.7 1990-92: 30.7	2.5% 6.7% 6.9% 7.1%	[16]
82-85	USA	1 teaching hospital	48/4	12		[76]
83-86	USA	1 university hospital	135/4	1983: 23 1984-85: 32 1986: 46	4.6% 6.2 %	[13]
86-91	USA	1 teaching hospital	106/5.8	1986: 5 1987-88: 14 1989: 32 1990-91: 20.5		[44]
88-89	USA	1 hospital	106/1	106		[17]
88-92	USA	1 cancer center	491/4	122.8		[34]
90-94	USA	4 university hospitals	427/4.5	23.7		[46]
87-89	USA	1 hospital	374/5	1987-89: 53 1991-92: 107	4-5% 6-6.5%	[32]
92-93	USA	2 hospitals	60/1	30	5.9%	[2]
92-93	USA	87 hospitals	837/2	4.8		[43]
95-98	USA	49 hospitals	934/3	6.4	7.6 %	[38]
95-96	USA	50 hospitals	379/1.2	6.5	8%	[77]
97-98	USA	22 hospitals	409/2	9.3		[42]
86-93	Canada	1 tertiary care hospital	98/7	14	6.5%	[47]
85-96	Canada	1 university hospital	318/12	26.5	Before 1986: <2% 1986-90: 2-3% 1991-96: 4-6%	[20]
92-94	Canada	14 hospitals	415/2	14.8		[49]
97-98	Canada	5-6 hospitals	118/2	9.8		[42]
92-96	Belgium	117 hospitals (59% of all acute-care institutions)	867/4	1.9	5.6%	[50]
84-88	Denmark	1 university hospital	111/5	22.2	<1%	[27]
89-94	Denmark	1 university hospital	206/6	34.3		[28]
96-98	Denmark	7 hospitals	48/3	2.3	1.5%	[78]
79-89	Germany	1 university hospital	35/4	1979: 3 1982: 4 1986: 18 1989: 10	1.3% 1.6% 6.7% 3.2%	[21]
83-85	Germany Austria	15 hospitals	166/2	5.5	1.9%	[51]
87-95	Netherlands	5 university hospitals	626/9	1987-89: 10.7 1990-92: 12.9 1993-95: 18.1		[22]
74-89	Norway	1 university hospital	27/7	1974-79: 1.2 1988-89: 10	1% 2.2%	[26]
77-81	Norway	1 university hospital	18/5	3.6		[25]
91-96	Norway	All major hospitals in Norway	560/6	4.2		[24]
89-98	Slovakia	71 hospital	288/10	0.4		[23]
70-82	Sweden	Hospitals in the Gothenburg area	200/13	< 10		[53]
80-86	Switzerland	1 university hospital	52/6	8.7	2 %	[52]
83-94	Italy	1 cancer hospital (university clinic)	113/12	1983-86: 3 1987-90: 8 1991-94: 17		[58]

Table 1. Number of candidemia episodes reported in studies from various countries. (cont.)

Year*	Country	Hospital	Candidemia episodes			Reference
			Total no. of episodes/ years	No. per year and per hospital	% of total no. of bloodstream infections	
73-83	Spain	ICU in 1 hospital	67/10.8	6.1		[60]
91-92	Spain	ICUs in 28 hospitals	46/1.3	1.3		[61]
94-97	Spain	34 hospitals	165/3.3	1.5	3.1	[79]
97	Spain	39 hospitals	143/0.3	14.7		[59]
92-94	Europe	30 tertiary care or university hospitals (cancer patients)	249/2	4.2 (range 1-18)		[35]
97-98	Europe	24 hospitals in 14 countries%	272/1.8	6.2	2.8%	[80]
97	Europe	20 hospitals in 13 countries	170/1	8.5 (range 2-30)		[81]
94	Israel	14 of 18 general hospitals in Israel	293/1	20.9		[37]
81-90	India	Nehru Hospital	60/10	6		[29]
91-95	India	Nehru Hospital	579/5	1991-92: 27 1993-94: 126 1995: 275		[30]
81-92	Japan	1 university hospital	113/12	9.4	1981-85: 13.9% 1986-88: 12.1 % 1989-92: 16.9 %	[63]
82-93	Japan	1 university hospital	44/12	1982-85: 3.5 1986-89: 2.5 1990-93: 5	9% 6 % 10 %	[36]
86-90	Japan	1 hospital (?)	84/6	14		[62]
89-93	Taiwan	National Taiwan university Hospital	215/13	16.5		[82]
94-95	Taiwan	National Taiwan university Hospital	147/1	147		[31]
95	Brazil	6 hospitals	73/0.8	14.6		[64]
95-96	Brazil	6 hospitals	145/1.8	13.2		[65]
94-95	Brazil	3 hospitals (cancer patients)	43/1.5	9.6		[67]
94-96	Brazil	1 hospital	83/2	41.5		[66]
97-98	Latin America	6-7 hospitals in Latin America	107/2	7.6		[83]

*Some studies performed for selected years and some studies for part of the period indicated.
% The first 20 consecutive blood culture isolates in each calendar month in each hospital

Japanese university hospital the average annual number of candidemia episodes was < 5 during the period 1982-1993 and this represented ≥ 6-10% of the total number of patients with bacteremia/fungemia [36].

A better comparison between studies can be made if the candidemia rate is correlated with the number of patients treated in the hospital. This has been done in a few studies by calculating the number of candidemia cases per 1,000 or 10,000 admissions (or discharges) or as the number of episodes per 10,000 patient days of care (Table 2). It is apparent that the rate varies enormously between hospitals and between hospital units. The candidemia rate per 1,000 admissions at the university hospital in Taiwan in 1994 [31] is for instance nearly 7.5 times higher than the average rate from NNIS study in 1990 [19,33] and 28 times higher than the average rate from Norway in 1996 [24]. The candidemia rates reported from intensive care units or specialized cancer units are usually high compared to the figures given for general surgery and internal medicine wards [37]. Even if the number of candidemia episodes is related to the number of patients admitted or treated, the type of institution may therefore have a strong influence on the result.

The rate per 100,000 population has also been calculated in some studies (Table 2). This is also a crude measure and highly dependent on the level of medical care in each country and it is probably impossible to compare rates between industrialized and non-industrialized countries.

All the different ways of calculating candidemia rates have apparent weaknesses. It would therefore be a great advantage if candidemia rates were reported in a way that makes comparisons between hospitals and countries possible. Until a better system is developed, this is probably best be achieved by reporting the number of cases in relation to the number of patients treated.

Available results do indicate that the candidemia rate is high in many hospitals in the United States compared to European hospitals. The high candidemia rate in this country has been documented in two later studies from hospitals participating in the SCOPE program (Surveillance and Control of Pathogens of Epidemiologic Importance). It was shown both in a one-year study from 1995-1996 and a later extension of the same study covering the years 1995-1998 that *Candida* was the fourth leading cause of nosocomial bloodstream infections, accounting for approximately 8% of all [38,39]. Some hospitals outside the United States, e.g. in India and Taiwan, also have a high number of candidemia cases. These differences compared to European hospitals are interesting, but the significance of the data should be evaluated further.

Species distribution of *Candida* bloodstream isolates

The various *Candida* species isolated from blood have a predictable susceptibility pattern to amphotericin B and fluconazole, the two most commonly used antifungal drugs for the treatment of invasive *Candida* infection. Most *Candida* species are susceptible to amphotericin B. Fluconazole is also active against most yeast species, but there are some important exceptions. *Candida krusei* and *Candida norvegensis* [40] isolates are resistant and many

Table 2. Rate of candidemia in various studies

Year	Country	Hospital(s)	Candidemia rate per:			Reference
			1,000 admissions or discharges	10,000 patient days	100,000 population	
89-90	USA	124 hospitals	All hospitals: 0.5 Non teach[#]: 0.28 Small teach: 0.37 Large teach: 0.61			[19,33]
91	USA	1 university hospital		2		[16]
88-92	USA	1 cancer center	6			[34]
92-93	USA	87 hospitals			8	[43]
93-95	USA	7 SICU[¤] and 6 NICU[$]	SICU: 9.82 NICU: 12.29	SICU: 9.9 NICU: 6.4		[45]
86-93	Canada	1 tertiary care hospital	0.49			[47]
92-94	Canada	14 hospitals			District 1[&]: 5.14 District 2: 3.53 District 3: 1.18	[49]
95	Netherlands	5 university hospitals		0.72		[22]
96	Norway	All major hospitals in Norway	All hospitals: 0.17	All hospitals: 0.26 University: 0.36 County: 0.19	2.17	[24]
94	Italy	1 cancer hospital (university clinic)	Approx. 21			[58]
94	Israel	14 of 18 general hospitals in Israel	All patients: 0.43 Surg/med[*]: 0.4-0.5 ICU: 6 NICU: 8			[37]
93	Taiwan	National Taiwan University Hospital	All patients: 2.19			[82]
94	Taiwan	National Taiwan University Hospital	All patients: 3.7 SICU: 94 MICU[$]: 63.4			[31]

[#] teach: teaching hospitals
[¤] SICU: Surgical intensive care unit
[£] NICU: neonatal intensive care unit
[&] District 1: Hamilton and Burlington, District 2: Manitoba, District 3: Ottawa
[*] Surg/med: General surgery and internal medicine
[$] MICU: Medical intensive care unit

Candida glabrata isolates have reduced susceptibility. A correct species identification of an isolate will therefore provide important information as to the probable susceptibility to fluconazole. Since antifungal treatment is often started on the basis of clinical suspicion alone it is important to know how frequent species with reduced susceptibility or resistance is occurring. The results from a majority of the studies done on species distribution of candidemia isolates in various countries are summarized in Table 3.

Species distribution in different countries

United States. Many studies have been reported from the United States. *C. albicans* is the most prevalent species. In 24 studies *C. albicans* accounted for between 38,8% and 79,4% of candidemia cases (Table 3), but in only three of these studies did it exceed 60% [17,32,41]. In a recent study from 49 hospitals across the country *C. albicans* accounted for approximately 50% in three of the regions (northeast, northwest and southeast), while 70% of 164 isolates in the southeast region belonged to this species [38].

The three most prevalent non-*albicans* species are *C. glabrata*, *C. tropicalis* and *C. parapsilosis*. In recent studies *C. glabrata* accounts for 20 to 25% of candidemia episodes [2,32,38,42]. *C. tropicalis* is usually somewhat less prevalent (approximately 10%) [42-45]. A few hospitals do, however, have a percentage of *C. tropicalis* isolates between 15 and 20% [17,32,34,46]. In most recent studies the proportion of *C. parapsilosis* strains has been between 10 and 20% whereas the incidence of *C. krusei* isolates is low (approximately 4%).

Canada. Studies from Canada show a different picture from the United States. In five of six studies the *C. albicans* percentage is above 60% (62-74%) [20,42,47-49]. The non-*albicans* species are correspondingly less prevalent; *C. parapsilosis* and *C. glabrata* approximately 10% each and *C. tropicalis* between 2 and 10%. (Table 3).

Europe. The high prevalence of *C. albicans* in Canada resembles the occurrence of this species in some European countries. Recent studies from Belgium [50], Denmark [28], and Norway [24] all show a high proportion of *C. albicans* (approximately 70%) (Table 3). In older studies from Germany [51], Switzerland [52] and Sweden [53] the proportion of *C. albicans* isolates was equally high. In The Netherlands [22] and the Slovak Republic [23] the occurrence of *C. albicans* seems to be somewhat lower (60%) than in the above European countries.

An interesting finding from Denmark and Norway is the occurrence of *C. norvegensis.* In these two countries *C. norvegensis* is regularly found to cause a small number of serious infections [27,40,54-56], but has otherwise only been reported from England [57].

Table 3. Distribution of *Candida* species isolated from blood culture.

Year[&]	Country	No of isolates[*]	Species - % of isolates										Reference
			C. albicans	*C. tropicalis*	*C. parapsilosis*	*C. glabrata*	*C. krusei*	*C. guillermondii*	*C. lusitaniae*	*C. norvegensis*	*Candida* sp	Other or not identified	
72-81	USA	226	45	25	13	15	1		0.4		1		[14]
72-77	USA	85	52	13	4	0	6				6	20	[72]
74-77	USA	129	41	23	12	20	3				1		[69]
75-81	USA	64	55	17	19	8	2						[84]
76-83	USA	117	62	12	24	0					2		[41]
78-82	USA	200	45	26	12	11	4				4		[12]
78-79	USA	71	48	27	10	14	1						[74]
80-89	USA	232	56	16	11	10	0.4	0.4	1		1	4	[75]
82-85	USA	51	55	24	14	6			2				[76]
83-86	USA	135	51	25	12	9					3		[13]
84-92	USA	642	57	8	12	17						8	[15]
86-91	USA	108	55	10	16	10	2	1	2		5		[44]
88-89	USA	106	63	17	6	13	1						[17]
88-92	USA	479	42	18	18	11	4	0.6	2		4	1	[34]
90-94	USA	441	52	15	11	6	4		1		0.5		[46]
87-89	USA	160	79	4	8	10							[32]
91-92	USA	214	39	20	16	26							[32]
92-93	USA	60	50			25					25		[2]
92-93	USA	837	52	10	21	12	4	2	0.6		0.1		[43]
93-95	USA	77	55	10	17	16					3		[45]
95-98	USA	929	53	12	10	20	3				2		[38]
95-96	USA	379	52	11	8	20	5				4		[77]
97	USA	203	56	7	9	19	3				7		[42]
98	USA	206	54	6	15	22	1				2		[42]
86-93	Canada	102	74	3	7	8	1		2				[47]
85-96	Canada	318	62	12	12	8	3	1	1		2		[20]
91-94	Canada	100	73	2	8	13		1			3		[48]
92-94	Canada	415	69	7	10	8	1	0.2	0.7		4		[49]
97	Canada	61	53	8	23	12	2				3		[42]
98	Canada	57	70	5	7	12	2				4		[42]
92-96	Belgium	867	68								32		[50]
84-88	Denmark	111	79	5	5	5	2	2	1	2	1		[27]
89-94	Denmark	206	72	8	4	8	4		2		2		[28]
79-89	Germany	35	46	17	9	3					26		[21]
83-85	Germany Austria	166	65	12	9	10	0.6	2			1		[51]
87-89	Netherlands	161	72	3	4	7	2	0.6			0.6	11	[22]
90-92	Netherlands	194	68	3	5	5	0.5	1			5	13	[22]
93-95	Netherlands	271	61	4	4	15	2	2			3	10	[22]
91-93	Norway	279	68	7	11	12	1	1			0.4	0.7	[24]
94-96	Norway	281	69	6	5	14	3	0.7	0.4	0.7	1	0.4	[24]
89-95	Slovakia	116	77	6	7	3	6	1					[23]
96-98	Slovakia	172	59	4	13	4	6	2	2		11		[23]
70-82	Sweden	199	71	2	11	14					2		[53]
80-86	Switzerland	52	71	2	2	10	6				10		[52]
83-90	Italy	45	33	16	24		16	11					[58]
91-94	Italy	68	28	6	35		7	13			10		[58]
88-97	Italy	74	42	24	5	5	15	5			3		[85]
73-83	Spain	67	48	5	3	5					40		[60]
91-92	Spain	47	60	9	17	2	2				11		[61]
97	Spain	143	41	7	37	6	4	3	1		1		[59]
92-94	Europe	249	49	11	11	10	9	4	2	0.4	4.0		[35]
97	Europe	170	53	6	21	12	1	4			3		[81]
94	Israel	293	54	11	12	7	0.7	0.3			16		[37]
89	South Africa	103	43	27	20	8	1	1					[86]
81-90	India	60	50	15	8	3	2	17			5		[29]
91-95	India	579	25	42	6	2	10	15					[30]
81-92	Japan	113[#]	25	14	26	8							[63]
82-93	Japan	44	25	11	21	16	2	2	2		21		[36]
86-90	Japan	84[&]	39	12	20	11		5					[62]
89-93	Taiwan	215[&]	49	17	14	10							[82]
94-95	Taiwan	120	50	20	9	14	2	3			3		[31]
95	Brazil	73	23	29	34	4	1	7			1		[64]
95-96	Brazil	145	37	24	25	4	1	2			7		[65]
94-95	Brazil	33	18	49	18			12	3				[67]
94-96	Brazil	83	52	12	18	2	1	10			5		[66]
97	Latin America	42	41	12	38	2		2			5		[83]
98	Latin America	65	45	20	19	9	2				6		[42]

[&] The results for some studies covering many years have been divided into two or more time periods.
[*] Number of *Candida* species isolates; other yeasts or unidentified yeast isolates are included for some of the studies
[#] Includes all fungemia episodes

Large, comprehensive studies seem to be lacking from other European countries. The species distribution was quite unusual in one study from a cancer institution in Italy for the years 1983-1994. [58]. The proportion of *C. albicans* was low (30%) while the proportions of *C. parapsilosis* (31%), *C. guillermondii* (12%) and *C. krusei* (10%) isolates were quite high. A multicenter study on cancer patients in 30 tertiary care or university medical centers located in Europe, mainly in France, Italy and Belgium (n = 28) and in Israel and Saudi Arabia (n = 2), also showed quite a low proportion (49%) of *C. albicans* isolates [35]. *C. glabrata, C. tropicalis, C. parapsilosis* and C. *krusei* accounted for 9 – 11% each. Approximately 1/3 of these patients had, however received absorbable antifungal drugs before the occurrence of candidemia. It is, however, not likely that the results of these two studies from specialized cancer institutions reflects the situation in these countries as a whole.

A recent study from Spain [59] may indicate that the species distribution in this country is different from Northern Europe. A survey was done in 39 hospitals during three months in 1997. The prevalence of *C. albicans* was low (41%) while the *C. parapsilosis* prevalence was high (37%). Similarly the *C. albicans* percentage was low (< 50%) in Spain in an earlier study from 1973-1983 [60]. However, in a 15-month study from ICUs in 28 hospitals in Spain *C. albicans* accounted for 60% of the episodes [61].

South America, Japan, Taiwan and India. Studies from South America, Japan, Taiwan and India are all quite consistent in that the prevalence of *C. albicans* is much lower than in Canada and Northern Europe. In a study from India the proportion of *C. albicans* was 25% while the proportion of non-*albicans* species was: *C. tropicalis* - 42%, *C. guillermondii* - 15% and *C. krusei* - 10% [30]. Three studies from Japan all show a low prevalence of *C. albicans* (25-40%) and quite a high proportion of *C. parapsilosis* (20-26%) [36,62,63].

Studies from Latin America are comparatively few, but it seems that the proportion of *C. albicans* isolates is low, *C. parapsilosis* quite high and that *C. glabrata* is a rarely occurring species [64-67]. A multicenter study which included 534 fungal blood culture isolates from 30 laboratories in 8 countries did also show that the occurrence of *C. albicans* was low in Latin America: Argentina 53%, Brazil 12.5%, Colombia 16%, and Venezuela 45% [68]. It should, however, be noted that the number of patients included in these studies is quite few.

Even though the number of studies is limited from many geographical regions, the results strongly indicate that there are marked variations in the occurrence of the most important yeast species and that these differences existed before the introduction of fluconazole. For many years the occurrence of *C. albicans* has for instance been quite different in the United States as compared to Canada and many European countries. It is probable that this reflects regional variations in the normal human yeast flora.

In addition to the differences between countries there are also differences between hospitals. This is demonstrated by results from many of the studies in the United States. Such variability could for instance be explained by differences in the patient populations, the amount of antifungal drugs used for prophylaxis and treatment and perhaps also by antibiotic usage. It is therefore important that the distribution of *Candida* species causing serious infections is monitored in each hospital.

Change in species distribution over time?

Except for the United States the number of candidemia studies covering an extended period of time are few. In 21 of 24 studies from the United States covering the period 1972 – 1998 *C. albicans* account for between 40 and 56% of the yeast species irrespective of when the studies were performed. In six studies the proportion of *C. albicans* was lower than 50% and four of these studies were performed before 1985. The proportion of the most important non-*albicans* species has, however, varied quite a lot. *C. tropicalis* was prevalent in earlier studies. In six studies before 1985 approximately 25% of all strains belonged to this species. In the 1990s the proportion of *C. tropicalis* isolates seems to have decreased in most hospitals [15,38,42-45]. The proportion of *C. glabrata* isolates has on the other hand increased in latter years. With a few exceptions [14,69] most of the earlier studies have a low proportion of *C. glabrata* isolates (less than 10-12%) (Table 3). This has changed recently in that *C. glabrata* strains now accounts for 20 – 25% of all the *Candida* species causing candidemia [2,32,38,42].

The studies from the United States therefore indicate that the proportion of *C. albicans* isolates has been quite constant for many years. The distribution of non-*albicans* species has, however, changed in that *C. tropicalis* now is less prevalent while *C. glabrata* is on the increase.

In studies from the Netherlands, Norway and from Denmark the species distribution have been followed for a prolonged period of time [22,24,27,28]. In the two studies from Denmark which covers one large university hospital from 1984 to 1994 [27,28] and in the study from Norway which included all major hospitals in the country from 1991 to 1996, the distribution of species is remarkably constant throughout the periods surveyed [24]. The study from the Netherlands do, however, show a reduction of *C. albicans* rates from 72% to 60.5% and an increase in *C. glabrata* rates from 6.8% to 14.8% from 1987 to 1995 (Table 3) [22].

The proportion of *C. albicans* isolates did also decreased in a national study from Slovakia for the years 1989 – 1998 [23]. *C. albicans* accounted for 77% of the 116 candidemia isolates in the first seven years of the study compared to 59% of 172 isolates in the next three years [23].

Two studies from one hospital in India [29,30] show a remarkable change in the distribution of species. The first 10 years *C. albicans* accounted for 50%, but this decreased to 25% the next 5 years. There was a parallel increase in *C. tropicalis* from 15% to 42% and *C. krusei* from 2% to 10%. The proportion of *C. guillermondii* was high (15-16%) in both study periods.

Even though few long-term studies have been done it seems that a shift in species distribution has occurred in a few countries, but has remained remarkably stable in other. The reason for these differences is not known. It is of course possible that the widespread use of fluconazole in hospitals have played a role [32,34,70]. If fluconazole prophylaxis is effective, it is to be expected that prophylaxis will exert a selection pressure.

Conclusions

Prospective, long-term nationwide candidemia studies are few. It is, however, documented that the candidemia rate has increased during the last 10-20 years in many tertiary care hospitals. It is not known to what an extent an

increase also has occurred in smaller, non-specialized hospitals. In some hospitals the candidemia rate has increased quite markedly in a short time span. The reason for this is unknown.

The candidemia rate in the United States seems to be higher than in most European hospitals. A few hospitals in other countries also have a high number of *Candida* bloodstream isolates. Comparison between countries is, however, difficult because of lack of data.

The distribution of *Candida* species isolated from blood varies markedly between different geographical regions in the world. The reason for this is unknown, but may be due to differences in the normal human yeast flora.

References

1. Edwards JE Jr, Bodey GP, Bowden RA, *et al.* International Conference for the Development of a Consensus on the Management and Prevention of Severe *Candida*l Infections. Clin Infect Dis 1997;25:43-59.
2. Weinstein MP, Towns ML, Quartey SM, *et al.* The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. Clin Infect Dis 1997;24:584-602.
3. Bernhardt HE. Disseminated candidiasis in surgical patients. Surg Gynecol Obstet 1972;134:819-825.
4. Berenguer J, Buck M, Witebsky F, Stock F, Pizzo PA, Walsh TJ. Lysis-centrifugation blood cultures in the detection of tissue-proven invasive candidiasis: disseminated versus single organ infection. Diagn Microbiol Infect Dis 1993;17:103-109.
5. Sandven P, Hoiby EA. The importance of blood volume cultured on detection of bacteraemia. Acta Pathol Microbiol Scand B 1981;89:149-152.
6. Tenney JH, Reller LB, Mirrett S, Wang WL, Weinstein MP. Controlled evaluation of the volume of blood cultured in detection of bacteremia and fungemia. J Clin Microbiol 1982;15:558-561.
7. Guerra-Romero L, Edson RS, Cockerill FR, III, Horstmeier CD, Roberts GD. Comparison of Du Pont Isolator and Roche Septi-Chek for detection of fungemia. J Clin Microbiol 1987;25:1623-1625.
8. Murray P. Comparison of the lysis-centrifugation and agitated biphasic blood culture systems for detection of fungemia. J Clin Microbiol 1991;29:96-98.
9. Fridkin SK, Jarvis WR. Epidemiology of nosocomial fungal infections. Clin Microbiol Rev 1996;9:499-511.
10. Pfaller MA, Messer SA, Houston A, *et al.* National epidemiology of mycoses survey: a multicenter study of strain variation and antifungal susceptibility among isolates of *Candida* species. Diagn Microbiol Infect Dis 1998;31:289-296.
11. McGowan JE Jr, Barnes MW, Finland M. Bacteremia at Boston City Hospital: Occurrence and mortality during 12 selected years (1935-1972), with special reference to hospital-acquired cases. J Infect Dis 1975;132:316-335.
12. Horn R, Wong B, Kiehn TE, Armstrong D. Fungemia in a cancer hospital: changing frequency, earlier onset, and results of therapy. Rev Infect Dis 1985;7:646-655.
13. Komshian SV, Uwaydah AK, Sobel JD, Crane LR. Fungemia caused by *Candida* species and *Torulopsis glabrata* in the hospitalized patient: frequency, characteristics, and evaluation of factors influencing outcome. Rev Infect Dis 1989; 11:379-390.
14. Bille J, Stockman L, Roberts GD. Detection of yeasts and filamentous fungi in blood cultures during a 10-year period (1972 to 1981). J Clin Microbiol 1982;16:968-970.
15. Cockerill FR, Hughes JG, Vetter EA, *et al.* Analysis of 281,797 consecutive blood cultures performed over an eight-year period: trends in microorganisms isolated and the value of anaerobic culture of blood. Clin Infect Dis 1997;24:403-418.
16. Pittet D, Wenzel RP. Nosocomial bloodstream infections. Secular trends in rates, mortality, and contribution to total hospital deaths. Arch Intern Med 1995;155:1177-1184.
17. Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dunagan WC. Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. Clin Infect Dis 1992;15:414-421.
18. Beck Sague C, Jarvis WR. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980-1990. J Infect Dis 1993;167:1247-51.
19. Jarvis WR. Epidemiology of nosocomial fungal infections, with emphasis on *Candida* species. Clin Infect Dis 1995;20:1526-1530.
20. Karlowsky JA, Zhanel GG, Klym KA, Hoban DJ, Kabani AM. Candidemia in a Canadian tertiary care hospital from 1976 to 1996. Diagn Microbiol Infect Dis 1997;29:5-9.
21. Geerdes HF, Ziegler D, Lode H, *et al.* Septicemia in 980 patients at a university hospital in Berlin: prospective studies during 4 selected years between 1979 and 1989. Clin Infect Dis 1992;15:991-1002.
22. Voss A, Kluytmans JA, Koeleman JG, *et al.* Occurrence of yeast bloodstream infections between 1987 and 1995 in five Dutch university hospitals. Eur J Clin Microbiol Infect Dis 1996;15:909-912.
23. Krcmery V, Jr., Kovacicova G. Longitudinal 10-year prospective survey of fungaemia in Slovak Republic: trends in etiology in 310 episodes. Slovak Fungaemia study group. Microbiol Infect Dis 2000;36:7-11.
24. Sandven P, Bevanger L, Digranes A, Gaustad P, Haukland HH, Steinbakk M. Constant low rate of fungemia in Norway, 1991 to 1996. J Clin Microbiol 1998;36:3455-3459.
25. Maeland A. Fungemia. Case records from Ulleval Hospital. Tidsskr Nor Laegeforen 1983;103:1063-1066.
26. Haug JB, Harthug S, Kalager T, Digranes A, Solberg CO. Bloodstream infections at a Norwegian university hospital, 1974- 1979 and 1988-1989: changing etiology, clinical features, and outcome. Clin Infect Dis 1994;19:246-256.
27. Nielsen H, Stenderup J, Bruun B. Fungemia in a university hospital 1984-1988. Clinical and mycological characteristics. Scand J Infect Dis 1991;23:275-282.
28. Bruun B, Westh H, Stenderup J. Fungemia: An increasing problem in a Danish university hospital 1989 to 1994. J Clin Microbiol Infect 1995;1:124-126.
29. Chakrabarti A, Chander J, Kasturi P, Panigrahi D. Candidaemia: a 10-year study in an Indian teaching hospital. Mycoses 1992;35:47-51.
30. Chakrabarti A, Ghosh A, Batra R, Kaushal A, Roy P, Singh H. Antifungal susceptibility pattern of non-*albicans Candida* species & distribution of species isolated from candidaemia cases over a 5 year period. Indian J Med Res 1996;104:171-176.
31. Hung CC, Chen YC, Chang SC, Luh KT, Hsieh WC. Nosocomial candidemia in a university hospital in Taiwan. J Formos Med Assoc 1996;95:19-28.
32. Price MF, LaRocco MT, Gentry LO. Fluconazole susceptibilities of *Candida* species and distribution of species recovered from blood cultures over a 5-year period. Antimicrob Agents Chemother 1994;38:1422-1427.
33. Banerjee SN, Emori TG, Culver DH, *et al.* Secular trends in nosocomial primary bloodstream infections in the United States, 1980-1989. Am J Med 1991;91:86S-89S.
34. Abi-Said D, Anaissie E, Uzun O, Raad I, Pinzcowski H, Vartivarian S. The epidemiology of hematogenous candidiasis caused by different *Candida* species. Clin Infect Dis 1997;24:1122-1128.
35. Viscoli C, Girmenia C, Marinus A, *et al.* Candidemia in cancer patients: a prospective, multicenter surveillance study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC). Clin Infect Dis 1999;28:1071-1079.
36. Mizushima Y, Li H, Yoshida I, Oosaki R, Kobayashi M. Changes in clinical features of fungemia in a Japanese University Hospital over a 12-year period. Intern.Med. 1996;35:707-711.
37. Rennert G, Rennert HS, Pitlik S, Finkelstein R, Kitzes-Cohen R. Epidemiology of Candidemia—a nationwide survey in Israel. Infection 2000;28:26-29.
38. Edmond MB, Wallace SE, McClish DK, Pfaller MA, Jones RN, Wenzel RP. Nosocomial bloodstream infections in United States hospitals: a three- year analysis. Clin Infect Dis 1999;29:239-244.
39. Pfaller MA, Jones RN, Messer SA, Edmond MB, Wenzel RP. National surveillance of nosocomial blood stream infection due to *Candida albicans*: frequency of occurrence and antifungal susceptibility in the SCOPE Program. Diagn Microbiol Infect Dis 1998;31:327-332.
40. Sandven P, Nilsen K, Digranes A, Tjade T, Lassen J. *Candida norvegensis*: a fluconazole-resistant species. Antimicrob Agents Chemother. 1997;41:1375-1376.
41. Dyess DL, Garrison RN, Fry DE. *Candida* sepsis: Implications of polymicrobial blood-borne infection. Arch Surg 1985;120:345-348.
42. Pfaller MA, Jones RN, Doern GV, *et al.* Bloodstream infections due to *Candida* species: SENTRY antimicrobial survei-

llance program in North America and Latin America, 1997-1998. Antimicrob Agents Chemother 2000;44:747-751.
43. Kao AS, Brandt ME, Pruitt WR, *et al.* The epidemiology of candidemia in two United States cities: results of a population-based active surveillance. Clin Infect Dis 1999;29:1164-1170.
44. Debusk CH, Daoud R, Thirumoorthi MC, Wilson FM, Khatib R. Candidemia: current epidemiologic characteristics and a long- term follow-up of the survivors. Scand J Infect Dis 1994;26:697-703.
45. Rangel-Frausto MS, Wiblin T, Blumberg HM, *et al.* National epidemiology of mycoses survey (NEMIS): variations in rates of bloodstream infections due to *Candida* species in seven surgical intensive care units and six neonatal intensive care units. Clin Infect Dis 1999;29:253-258.
46. Nguyen MH, Peacock JEJ, Morris AJ, *et al.* The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. Am J Med 1996;100:617-623.
47. Taylor GD, Buchanan-Chell M, Kirkland T, McKenzie M, Wiens R. Trends and sources of nosocomial fungaemia. Mycoses 1994;37:187-190.
48. Phillips P, Shafran S, Garber G, *et al.* Multicenter randomized trial of fluconazole versus amphotericin B for treatment of candidemia in non-neutropenic patients. Canadian Candidemia Study Group. Eur J Clin Microbiol Infect Dis 1997;16:337-345.
49. Yamamura DL, Rotstein C, Nicolle LE, Ioannou S. Candidemia at selected Canadian sites: results from the Fungal Disease Registry, 1992-1994. Fungal Disease Registry of the Canadian Infectious Disease Society. CMAJ 1999;160:493-499.
50. Ronveaux O, Jans B, Carsauw H. Epidemiology of nosocomial bloodstream infections in Belgium, 1992-1996. Eur J Clin Microbiol Infect Dis 1998; 10:695-700.
51. Dermoumi H. Pilze als Sepsiserreger - Ergebnisse einer multizentrischen Studie. Mykosen 1987;30:349-354.
52. Zanetti G, Calandra T, de Muralt B, Bille J, Glauser MP. *Candida* fungemia. Schweiz Med Wochenschr 1989;119:1213-1218.
53. Eilard T. Isolation of fungi in blood cultures. A review of fungal infections in the western part of Sweden 1970-1982. Scand J Infect Dis 1987;19:145-156.
54. Dietrichson E. Etude d'une collection norvégienne de levures. Ann de Parasitologie 1954;24:460-498.
55. Nielsen H, Stenderup J, Bruun B, Ladefoged J. *Candida norvegensis* peritonitis and invasive disease in a patient on continuous ambulatory peritoneal dialysis. J Clin Microbiol 1990;28:1664-1665.
56. Nielsen H, Stenderup J. Invasive *Candida norvegensis* infection in immunocompromised patients. Scand J Infect Dis 1996;28:311-312.
57. Hood SV, Moore CB, Denning DW. Isolation of *Candida norvegensis* from clinical specimens: Four case reports. Clin Infect Dis 1996;23:1185-1187.
58. Girmenia C, Martino P, De Bernardis F, *et al.* Rising incidence of *Candida parapsilosis* fungemia in patients with hematologic malignancies: Clinical aspects, predisposing factors, and differential pathogenicity of the causative strains. Clin Infect Dis 1996;23:506-514.
59. Rodriguez-Tudela JL, Cuenca-Estrella M. A multicenter study on fungemia caused by yeasts in Spain (April-June, 1997). Rev Clin Esp 1999;199:356-361.
60. Sanchez Rodriguez C, Leon Regidor MA, Capell FS, Perez CA, Planes RA, Leon GC. Fungemia 1973-1983. Analysis of 67 patients. Med Clin (Barc) 1985;84:549-553.
61. Nolla-Salas J, Sitges-Serra A, Leon-Gil C, *et al.* Candidemia in non-neutropenic critically ill patients: analysis of prognostic factors and assessment of systemic antifungal therapy. Study Group of Fungal Infection in the ICU. Intensive Care Med 1997;23:23-30.
62. Nakazawa S, Mori T, Hibiya I, Oguri T. Analysis of 84 cases with fungemia. Kansenshogaku Zasshi 1992;66:612-619.
63. Yamakami Y, Tashiro T, Tokimatsu I, *et al.* Microbiological and clinical study of fungemia between 1981 and 1992. Kansenshogaku Zasshi 1995;69:890-894.
64. Colombo AL, Nucci M, Caiuby MJ, *et al.* High incidence of non-albicans candidemia despite rare use of azoles. 1996; abstr. J45, p. 226. *In* Program and abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, DC Program
65. Colombo AL, Nucci M, Salomao R, *et al.* High rate of non-albicans candidemia in Brazilian tertiary care hospitals. Diagn Microbiol Infect Dis 1999;34:281-286.
66. Costa SF, Marinho I, Araujo EA, Manrique AE, Medeiros EA, Levin AS. Nosocomial fungaemia: a 2-year prospective study. J Hosp Infect 2000;45:69-72.
67. Nucci M, Silveira MI, Spector N, Silveira F, Velasco E, Martins CA, Derossi A, Colombo AL, Pulcheri W. Fungemia in cancer patients in Brazil: predominance of non-albicans species. Mycopathologia 1998;141:65-68.
68. Sandven P. Multicountry candidemia survey. Clin Microbiol Infect 1997;3, suppl. 2:15-15.
69. Meunier-Carpentier F, Kiehn TE, Armstrong D. Fungemia in the immunocompromised host. Changing patterns, antigenemia, high mortality. Am J Med 1981;71:363-370.
70. Wingard JR, Merz WG, Rinaldi MG, Johnson TR, Karp JE, Saral R. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. N Engl J Med 1991;325:1274-1277.
71. McGowan JE, Jr.. Changing etiology of nosocomial bacteremia and fungemia and other hospital-acquired infections. Rev Infect Dis 1985;7 (Suppl 3):S357-70.
72. Klein JJ, Watanakunakorn C. Hospital-acquired fungemia. Its natural course and clinical significance. Am J Med 1979;67:51-58.
73. Burchard KW, Minor LB, Slotman GJ, Gann DS. Fungal sepsis in surgical patients. Arch Surg 1983;118:217-221.
74. Hopfer RL, Orengo A, Chesnut S, Wenglar M. Radiometric detection of yeasts in blood cultures of cancer patients. J Clin Microbiol 1980;12:329-331.
75. Weber DJ, Rutala WA, Samsa GP, Wilson MB, Hoffmann KK. Relative frequency of nosocomial pathogens at a university hospital during the decade 1980 to 1989. Am J Infect Control 1992;20:192-197.
76. Harvey RL, Myers JP. Nosocomial fungemia in a large community teaching hospital. Arch Intern Med 1987;147:2117-2120.
77. Pfaller MA, Jones RN, Messer SA, Edmond MB, Wenzel RP. National surveillance of nosocomial blood stream infection due to species of *Candida* other than *Candida albicans*: frequency of occurrence and antifungal susceptibility in the SCOPE Program. Diagn Microbiol Infect Dis 1998;30:121-129.
78. Schønheyder HC. Two thousands seven hundred and thirty nine episodes of bacteremia in the county of Northern Jutland 1996-1998. Presentation of a regional clinical database. Ugeskr Laeger 2000;162:2886-2891.
79. Sota M, Ezpeleta C, Cisterna R. Description of 165 episodes of fungemia: a multicenter study. Rev Iberoam Micol 1999;16:30-35.
80. Fluit AC, Jones ME, Schmitz FJ, Acar J, Gupta R, Verhoef J. Antimicrobial Susceptibility and Frequency of Occurrence of Clinical Blood Isolates in Europe from the SENTRY Antimicrobial Surveillance Program, 1997 and 1998. Clin Infect Dis 2000;30:454-460.
81. Pfaller MA, Jones RN, Doern GV, *et al.* International surveillance of blood stream infections due to *Candida* species in the European SENTRY Program: species distribution and antifungal susceptibility including the investigational triazole and echinocandin agents. Diagn Microbiol Infect Dis 1999;35:19-25.
82. Chen YC, Chang SC, Sun CC, Yang LS, Hsieh WC, Luh KT. Secular trends in the epidemiology of nosocomial fungal infections at a teaching hospital in Taiwan, 1981 to 1993. Infect Control Hosp Epidemiol 1997;18:369-375.
83. Pfaller MA, Jones RN, Doern GV, Sader HS, Hollis RJ, Messer SA. International surveillance of bloodstream infections due to *Candida* species: frequency of occurrence and antifungal susceptibilities of isolates collected in 1997 in the United States, Canada, and South America for the SENTRY Program. The SENTRY Participant Group. J Clin Microbiol 1998;36:1886-1889.
84. Burchard KW, Minor LB, Slotman GJ, Gann DS. Fungal sepsis in surgical patients. Arch Surg 1983;118:217-221.
85. Pagano L, Antinori A, Ammassari A, *et al.* Retrospective study of candidemia in patients with hematological malignancies. Clinical features, risk factors and outcome of 76 episodes. Eur J Haematol 1999;63:77-85.
86. Badenhorst L, Botha PL, van Rensburg MN. The incidence of hospital fungal infections—yeast fungaemia. S Afr Med J 1991;79:302-303.