JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 1998, p. 3455–3459 Vol. 36, No. 12
0095-1137/98/$04.00+0

Constant Low Rate of Fungemia in Norway, 1991 to 1996

PER SANDVEN,[1]* LARS BEVANGER,[2] ASBJØRN DIGRANES,[3] PETER GAUSTAD,[4] HANNE H. HAUKLAND,[5] MARTIN STEINBAKK,[6] AND THE NORWEGIAN YEAST STUDY GROUP†

Department of Bacteriology, National Institute of Public Health, 0462 Oslo,[1] Department of Microbiology, Regional Hospital, Norwegian University of Science and Technology, 7006 Trondheim,[2] Department of Microbiology and Immunology, Haukeland Hospital, 5021 Bergen,[3] Microbiological Institute, National Hospital, University of Oslo, 0027 Oslo,[4] Department of Microbiology, University Hospital, 9038 Tromsø,[5] and Department of Microbiology, Ullevål University Hospital, 0407 Oslo,[6] Norway

Received 10 April 1998/Returned for modification 20 July 1998/Accepted 30 August 1998

Since 1991 information on yeast isolates from blood cultures has been recorded prospectively from all microbiological laboratories (5 university and 16 county or local hospital laboratories) in Norway (population, 4.3 million). From 1991 to 1996 a total of 571 episodes of fungemia in 552 patients occurred (1991, 109 episodes; 1992, 81 episodes; 1993, 93 episodes; 1994, 89 episodes; 1995, 98 episodes; and 1996, 101 episodes). The fungemia rates per 10,000 patient days were 0.29 in 1991 and 0.27 in 1996. The average rates for the years 1991 to 1996 were 0.37 for the university laboratories and 0.20 for the other laboratories. These rates are low compared to the rate (0.76) in five Dutch university hospitals in 1995 and the rate (2.0) in Iowa in 1991. The four most frequently isolated species were *Candida albicans* (66%), *Candida glabrata* (12.5%), *Candida parapsilosis* (7.6%), and *Candida tropicalis* (6.4%). The incidences of both *C. albicans* (range, 63 to 73%) and *C. glabrata* (range, 8.4 to 15.7%) varied somewhat throughout this period, but no significant increase or decrease was noted. MICs of amphotericin B, flucytosine, and fluconazole were determined for 89% of the isolates. All were susceptible to amphotericin B, and only 29 (5.6%) strains had decreased susceptibility to flucytosine. All *C. albicans* isolates were susceptible to fluconazole. The percentage of yeast isolates with decreased susceptibility to fluconazole (MICs, ≥16 μg/ml) did increase, from 9.6% in 1991 and 1992 to 12.2% in 1994, 16.1% in 1995, and 18.6% in 1996. This was largely due to increases in the percentages of resistant *C. glabrata* and *Candida krusei* strains in the last 2 years. Compared to the incidence in other countries, it is remarkable that Norway has such a low and constant incidence of fungemia. A possible reason for this difference might be a restricted antibiotic use policy in Norway.

Several studies, especially those from the United States, have shown that the incidence of fungal bloodstream infections has increased during recent years. It has, for instance, been shown by the National Nosocomial Infections Surveillance (NNIS) system for U.S. hospitals that the proportion of bloodstream infections caused by fungal pathogens increased from 5.4% in 1980 to 9.9% in 1990 (6). An increase in fungal bloodstream infections has also been reported from hospitals outside the United States (7, 8, 14, 33).

In view of this increasing importance of fungal infections reported from other countries, it was agreed in 1990 that all microbiological laboratories in Norway should participate in a prospective fungemia study. The specific objectives of the study should be threefold: (i) to define the incidence of fungal bloodstream infections in Norway, (ii) to identify the spectrum of pathogens causing yeast bloodstream infections, and (iii) to obtain antifungal susceptibility data for Norwegian bloodstream isolates. This report presents the data from this study for the period from 1991 to 1996.

MATERIALS AND METHODS

The medical microbiological laboratory network in Norway consists of 5 regional laboratories (all university hospitals), 13 county laboratories, and 3 hospital laboratories. These laboratories cover the microbiology services for all hospitals in Norway. All the laboratories have participated in the study.

Most laboratories use an automated blood culture system such as BACTEC (Becton Dickinson Microbiology Systems) or BactAlert (Organon Teknika Corp.), but a few laboratories have also used nonautomated commercial blood culture systems. One laboratory used the lysis-centrifugation blood culture system (Isolator blood culture system; E. Merck, Darmstadt, Germany) on a routine basis for part of the study period. Identification of the yeast species isolated from a cultured blood specimen is carried out by most of the laboratories.

Episodes of fungemia among hospitalized patients were recorded in each laboratory. An episode of fungemia was defined as at least one blood culture positive for fungi. Episodes of fungemia in a single patient were considered distinct if they occurred at least 1 month apart.

Approximately 90% of the strains were sent to the Mycological Reference Laboratory at the National Institute of Public Health (NIPH), Oslo, for identification and susceptibility testing. The following investigations were done at NIPH.

Identification. Identification to the species level was based on germ tube production, microscopic morphology on cornmeal agar, carbohydrate fermentation and assimilation, and urease activity (29). The identification obtained by a

* Corresponding author. Mailing address: Department of Bacteriology, National Institute of Public Health, P.O. Box 4404 Torshov, N-0403 Oslo, Norway. Phone: 47 22 04 22 00. Fax: 47 22 04 25 18. E-mail: per.sandven@labmed.uio.no.

† The Norwegian Yeast Study Group consists of one representative from each clinical microbiological laboratory in Norway. The group includes E. H. Aandahl, Department of Microbiology, LIMIK, Lillehammer; T. Bergan, Department of Microbiology, Aker Hospital, Oslo; N. O. Hermansen, Department of Microbiology, Buskerud Central Hospital, Drammen; E. Holten, Department of Microbiology, Akershus Central Hospital, Nordbyhagen; J. Lassen, Department of Microbiology, Norwegian Radium Hospital, Oslo; T. Mannsåker, Department of Microbiology, Sogn and Fjordane Central Hospital, Førde; L. Mortensen, Nordland Central Hospital, Bodø; F. Müller, Bærum Hospital, Bærum; O. B. Natås, Rogaland Central Hospital, Stavanger; Å. K. Nordius, Department of Microbiology, Innherred Central Hospital, Levanger; E. Ragnhildstveit, Department of Microbiology, Østfold Central Hospital, Fredrikstad; T. Skarpaas, Department of Microbiology, Vest-Agder Central Hospital, Kristiansand; T. Thoresen, Vestfold Central Hospital, Tønsberg; Y. Tveten, A/S Telelab, Skien; and E. Vik, Department of Microbiology, Molde County Hospital, Molde.

TABLE 1. Episodes of bloodstream yeast infections in Norway from 1991 to 1996

Year	No. of episodes of fungemia	No. of episodes of fungemia per 1,000 discharges	No. of episodes of fungemia per 10,000 PD[a]		
			County hospitals	University hospitals	All hospitals
1991	109	0.20	0.21	0.43	0.29
1992	81	0.15	0.13	0.36	0.22
1993	93	0.17	0.16	0.40	0.25
1994	89	0.17	0.18	0.33	0.24
1995	98	0.17	0.26	0.26	0.26
1996	101	0.17	0.20	0.37	0.27
1991 to 1996	571	0.17	0.19	0.36	0.26

[a] PD, patient days of care.

conventional scheme was occasionally supported by using a commercial system, ATB 32 C (bioMérieux, Marcy l'Etoile, France).

Susceptibility testing. During the 6 years of this study the susceptibility testing methods used at NIPH have changed somewhat. From 1991 until the end of 1993 a microdilution method in broth was used for amphotericin B and flucytosine (25) and an agar dilution method was used for fluconazole (31). The agar dilution method has been found to give results comparable to those given by the reference broth dilution method proposed by the National Committee for Clinical Laboratory Standards (NCCLS) Subcommittee on Antifungal Susceptibility Testing (31).

Since the beginning of 1994 a colorimetric microdilution method based on NCCLS recommendations has been used (21). Several strains from the period from 1991 to 1993 have been retested for their susceptibilities to amphotericin B, flucytosine, and fluconazole by the colorimetric method. The following strains were selected for retesting according to the indicated criteria: strains for which the fluconazole MIC was ≥1.5 μg/ml or the flucytosine MIC was ≥2 μg/ml. In addition, all *Candida glabrata* strains were retested, irrespective of previous susceptibility test results.

The colorimetric broth microdilution method was performed as described by Pfaller and Barry (21). Testing was performed with twofold drug dilutions in RPMI 1640 medium (Sigma Chemical Co., St. Louis, Mo.) buffered to pH 7.0 with 0.165 M morpholinepropanesulfonic acid buffer (Sigma). The antimycotic stock solutions were diluted according to the recommendations of NCCLS (18). The final concentrations were as follows: amphotericin B, 0.03 to 16 μg/ml; flucytosine, 0.125 to 64 μg/ml; and fluconazole, 0.125 to 64 μg/ml. The microdilution method is based on the NCCLS recommendations, in which a spectrophotometric method of inoculum preparation with a concentration of 0.5×10^3 to 2.5×10^3 cells per ml in RPMI 1640 medium is used. Yeast inocula (100 μl) were added to each well of microdilution trays containing 100 μl of antimycotic solution (2× final concentration). An oxidation-reduction indicator (Alamar Blue; Alamar Biosciences, Inc., Sacramento, Calif.) was added to each well at the time of inoculation (25 μl of Alamar Blue per well). The trays were incubated in air at 35°C and were read after 24 and 48 h. Growth was indicated by a color change from dark blue to red. The colorimetric microdilution MIC was defined as the lowest concentration of the antimycotic agent preventing the development of a red color.

The recently published NCCLS breakpoint criteria (18, 26) have been used in this study.

RESULTS

During the 6 years from 1991 to 1996 a total of 571 episodes of fungemia in 552 patients occurred in Norway (Table 1). Five patients had mixed infections with two yeast isolates; a total of 576 yeast strains were therefore recovered (Table 2). Thirteen patients had two or more episodes of fungemia which occurred at least 1 month apart. Ten patients had two episodes of fungemia; the same yeast species was recovered from nine of these patients. Three patients had more than two episodes of fungemia: one patient with three episodes (all *Candida albicans*) over 6 months, one patient with four episodes (all *Candida parapsilosis*) over 8 months, and the last patient with five episodes (four *C. albicans* and one *C. glabrata*) over 9 months.

Of the 552 patients, 57% were male and 43% were female. The majority of the patients (63%) were older than 50 years; 34% were older than 70 years, and 29% were ages 50 to 69 years. Thirty-five patients (6%) were less than 1 year old.

TABLE 2. Yeast strains isolated from blood cultures in Norway from 1991 to 96

Yeast species	No. (%) of isolates						
	1991	1992	1993	1994	1995	1996	Total
C. albicans	75	53	59	65	64	64	380 (66.0)
C. glabrata	16	7	10	9	14	16	72 (12.5)
C. parapsilosis	11	10	8	4	6	5	44 (7.6)
C. tropicalis	3	6	10	5	4	9	37 (6.4)
C. krusei	0	1	2	1	5	2	11 (1.9)
Candida guillermondii	1	2	1	0	0	2	6 (1.0)
Cryptococcus neoformans	1	0	1	0	2	1	5 (0.9)
Candida kefyr	0	0	0	0	2	1	3 (0.5)
Candida norvegensis	0	0	0	0	1	1	2 (0.3)
Other species[a]	3	2	3	4	0	1	13 (2.3)
Yeast not identified	0	2	0	1	0	0	3 (0.5)
Total	110	83	94	89	98	102	576

[a] Other species included *Candida blankii*, *Candida inconspicua*, *Candida lusitaniae*, *Candida sake*, *Candida sphaerica*, *Cryptococcus uniguttulatus*, *Geotrichum capitatum*, *Blastoschizomyces capitatus*, *Malassezia pachydermatis*, *Malassezia furfur*, *Rhodotorula rubra*, *Saccharomyces cerevisiae*, and *Sporobolomyces hispanicus* (one isolate of each species).

The annual number of episodes of bloodstream yeast infections remained fairly constant at approximately 100 episodes per year (range, 81 to 109 episodes) (Table 1). During the 6 years of this study the participating hospitals delivered a total of 22,351,023 patient days of care, averaging 3,725,171 ± 48,833 (mean ± standard deviation) patient days per year. There were no increases in the rates of bloodstream yeast infections expressed as episodes per 10,000 patient days (Table 1) from 1991 to 1996. This is true both for large university hospitals and for the other hospitals. The number of fungemic episodes per 1,000 discharges also remained constant at 0.17.

The various fungal species isolated and the frequencies at which they occurred are listed in Table 2. The four most frequently isolated species were *C. albicans* (66%), *C. glabrata* (12.5%), *C. parapsilosis* (7.6%), and *Candida tropicalis* (6.4%). The incidences of both *C. albicans* (range, 63 to 73%) and *C. glabrata* (range, 8.4 to 15.7%) varied somewhat throughout this period, but no significant increase or decrease was noted. Bloodstream *C. parapsilosis* infections decreased from 10% in 1991 to 5% in 1996, while the incidence of *C. tropicalis* infections increased from 3% in 1991 to 9% in 1996. These differences were, however, not statistically significant (by the chi-square test, $P > 0.05$).

The MICs of amphotericin B, flucytosine, and fluconazole were determined for 513 (89%) of the 576 strains (Table 3). All these strains were susceptible to amphotericin B. Most strains were also susceptible to flucytosine; 10 (3%) *C. albicans* strains, 2 (3%) *C. glabrata* strains, and 1 (3%) *C. tropicalis* strain had decreased susceptibilities to flucytosine (MICs, ≥8 μg/ml). For all 11 *Candida krusei* strains flucytosine MICs were ≥16 μg/ml. The proportions of isolates with decreased susceptibility to flucytosine were below 1% in 1991 and 1992, 8.9% in 1993, 5.4% in 1994, 9.2% in 1995, and 5.2% in 1996.

The majority of *C. albicans*, *C. parapsilosis*, and *C. tropicalis* isolates were susceptible to fluconazole (Table 3). Of 415 isolates belonging to these three species one *C. parapsilosis* strain and two *C. tropicalis* strains had decreased susceptibilities to fluconazole (MICs, ≥16 μg/ml). All *C. krusei* strains were resistant to fluconazole (MICs, ≥64 μg/ml), and for 42 (64%) *C. glabrata* strains fluconazole MICs were ≥16 μg/ml. The

TABLE 3. Susceptibilities of 513 yeast isolates from blood cultures to antifungal agents

Antifungal agent	Species	No. of isolates	MIC (μg/ml)[a]		
			50%	90%	Range
Amphotericin B	*C. albicans*	336	0.5	0.5	0.03–1
	C. glabrata	66	0.5	1	0.03–1
	C. parapsilosis	44	0.5	1	0.03–1
	C. tropicalis	35	0.5	1	0.03–1
	C. krusei	11	1	1	0.25–1
	Other species	21	0.5	1	0.06–1
Fluconazole	*C. albicans*	336	0.5	1	0.25–4
	C. glabrata	66	16	64	1–128
	C. parapsilosis	44	1	1	0.25–16
	C. tropicalis	35	2	4	0.5–128
	C. krusei	11	64	64	64–128
	Other species	21	4	64	0.5–64
Flucytosine	*C. albicans*	336	0.25	0.5	0.064–64
	C. glabrata	66	0.125	0.25	0.064–16
	C. parapsilosis	44	0.125	0.5	0.064–1
	C. tropicalis	35	0.125	0.5	0.064–64
	C. krusei	11	16	32	16–32
	Other species	21	0.125	64	0.125–64

[a] 50% and 90%, MICs at which 50 and 90% of isolates, respectively, are inhibited.

proportions of yeast isolates with decreased susceptibility to fluconazole (MICs, ≥16 μg/ml) did, however, increase from 9.6% in 1991 and 1992 to 12.2% in 1994, 16.1% in 1995, and 18.6% in 1996. This was largely due to increases in the numbers of fluconazole-resistant *C. glabrata* and *C. krusei* strains in the last 2 years (in 1995, 7 *C. glabrata* strains and 5 *C. krusei* strains; in 1996, 13 *C. glabrata* strains and 2 *C. krusei* strains). For three of the four laboratories with the largest number of isolates (>40 isolates) during this period (all were university hospitals), the proportions of isolates with decreased susceptibility to fluconazole varied between 6 and 9%. The fourth laboratory had 14 (22%) isolates with decreased susceptibility to fluconazole.

DISCUSSION

Several studies from different parts of the world have shown that bloodstream fungal infections are increasing. In the United States this was noted in some hospitals nearly 20 years ago. Horn et al. (13) observed that the total number of episodes of fungemia increased by 31% in a large cancer hospital from the period from 1974 to 1977 compared to that from the period from 1978 to 1982. More comprehensive data from the hospitals participating in the NNIS system showed that the rate of nosocomial yeast infections increased markedly between 1980 and 1990 (6). The rate increased by 487% from 1980 to 1989 among large teaching hospitals and by 219% among small teaching hospitals. Among nonteaching hospitals increases of 75% for small hospitals and 370% for large hospitals were found (5). For the years from 1990 to 1992 *Candida* spp. were the fourth most common bloodstream pathogen among hospitals participating in the NNIS system (15). In some institutions in the United States yeasts now account for 10 to 15% of all microorganisms recovered from cultures of blood (10, 20, 34). Increases have also been reported in other countries. At the National Taiwan University Hospital, a 27-fold increase in bloodstream infections due to *Candida* spp. was found from 1980 to 1994, and since 1993 *Candida* spp. have become the most common cause of nosocomial bloodstream infections (14). A markedly increased incidence was also noted at a tertiary-care hospital in India, from 15 patients in 1991 to 275 patients in 1996 (8). Studies from a Danish university hospital showed a gradual increase in the annual incidence of fungemia, from 19 episodes in 1989 to 57 episodes in 1994 (7). In one university hospital in Norway *Candida* spp. accounted for 1% of the microorganisms isolated from blood during the period from 1974 to 1979 and 2.2% (seven isolates per year) of the microorganisms isolated from blood during the period from 1988 to 1989 (12). A retrospective study from five Dutch university hospitals found an increase from 57 bloodstream yeast infections in 1987 to 100 episodes in 1995 (33). The rate doubled from 1987 to 1995, reaching an incidence of 0.76 episodes (rate of candidemia, 0.72 episodes) per 10,000 patient days.

Our data show that the incidence of bloodstream yeast infections in Norway has remained constant at approximately 100 episodes per year for the period from 1991 to 1996. The number of episodes per 10,000 patient days is low (0.26) and also remained constant during those 6 years. As expected, there was a higher incidence at the university hospitals (0.36 episodes per 10,000 patient days) compared to that at the county hospitals (0.19 episodes per 10,000 patient days). The average incidence at the five university hospitals in Norway was 2.1-fold lower than the incidence reported for the five Dutch university hospitals (0.36 versus 0.76) in 1995 (33), and the incidence in 1991 at these five Norwegian hospitals was 4.7-fold less than the incidence at the University of Iowa Hospitals and Clinics for the same year (0.43 versus 2) (23).

Compared to the incidence in other countries it is remarkable that Norway has such a low incidence of fungemia and also that the fungemia rate has remained constant in the 6-year period from 1991 to 1996. Possible reasons for this difference might be a restricted antibiotic use policy in Norway (2) and perhaps also that the antibiotic use is different from that in many other countries. The recommended therapy for septicemia of unknown etiology is, for instance, still a combination of an aminoglycoside and penicillin. Aminoglycoside use might be important since this group of antibiotics has no impact on the anaerobic flora of the gut, and yeast overgrowth is therefore less likely to occur (16, 28). Voss et al. (33) also suggested that the restricted antibiotic use policy of Dutch physicians may be the reason for a comparatively low incidence of candiemia in Dutch university hospitals.

The various yeast species isolated from blood often have a predictable pattern of susceptibility to antifungal drugs. It is therefore important to know the species distribution of isolates causing fungemia in each country and, preferably, in each hospital. Studies from different parts of the world have shown that the occurrence of yeast species may vary quite a lot (4, 8, 11, 14, 17, 27, 30). Usually, *C. albicans* accounts for more than 50% of the yeast species isolated; but in one study from the United States (1) and one study from South Africa (4), *C. albicans* was isolated from 42% of patients, and in studies from India (8) and Brazil (11), *C. albicans* was isolated from only 25 and 20% of the patients, respectively.

Recently, it has also been reported from some institutions in the United States (1, 19, 24, 34) and also from other parts of the world (8, 9, 33) that there has been a shift in the *Candida* spp. associated with nosocomial bloodstream infections. In one institution in the United States *C. albicans* caused 80% of bloodstream candidal infections in 1984 but was responsible for fewer than 50% of these infections in 1991 (34). The number of infections caused by *C. tropicalis*, *C. parapsilosis*, and other *Candida* spp. increased. At the M. D. Anderson Cancer Center in Houston, Tex., a decrease in the incidence of *C.*

albicans and *C. tropicalis* infections and an increase in the incidence of *C. krusei* and possibly *C. glabrata* infections were found between 1988 and 1992 (1). A significant decrease in incidence among patients with leukemia was also observed at that institution over the study period. In the studies from The Netherlands, India, and Taiwan (8, 9, 33), a shift in the species distribution parallelled an increased incidence. The reason for this change in epidemiology is not clear. It has been related by some investigators to the introduction of fluconazole and its widespread use (1, 24, 36), but this view has been questioned (35). It is also unlikely that the differences in species distribution reported from various countries could be explained by fluconazole use alone.

In Norway *C. albicans* accounts for approximately two-thirds of the isolates causing fungemia (Table 2). This is comparable to the situation in Denmark (7). *C. glabrata* is, however, isolated more frequently in Norway than in many other countries. A similar high incidence was found at the start of this study in 1991 (14.5%) and at the end of the study (1995, 14.3%; 1996, 15.8%). It is unlikely that the high incidence in 1991 was caused by fluconazole use since this drug was just licensed for sale in Norway in 1991. The amount of fluconazole used in 1991 was 0.022 defined daily doses/1,000 inhabitants/day, and the amount used in 1996 was 0.044 defined daily doses/1,000 inhabitants/day (19a).

Some microbiological laboratories in Norway use an agar diffusion test to screen for resistance to antifungal drugs (31), but susceptibility testing is not usually performed. The reason for this is that the susceptibility patterns of yeast species isolated in Norway have been predictable and because routine susceptibility testing of yeast isolates has not been recommended (22). All blood culture isolates and also other "important" isolates are, however, sent to the reference laboratory for susceptibility testing. The results of this study, which covers approximately 90% of the blood culture isolates in Norway for the period from 1991 to 1996, confirms that the susceptibility pattern is still quite predictable. All isolates were susceptible to amphotericin B, and only 29 (5.6%) isolates had decreased susceptibility to flucytosine. All *C. krusei* isolates (11 isolates) and 10 of 336 *C. albicans* isolates were in this group. A much higher degree of resistance to flucytosine has been reported from other countries (3, 32). Susceptibility to fluconazole was as expected. All *C. albicans* isolates were susceptible, and all *C. krusei* isolates and approximately two-thirds of *C. glabrata* isolates had decreased susceptibilities to fluconazole. The proportion of yeast isolates with decreased susceptibility to fluconazole (MICs, $\geq$16 μg/ml) did, however, increase from 9.6% in 1991 to 18.6% in 1996. The proportion of resistant isolates (MICs, $\geq$64 μg/ml) was 1% in 1991 and 5.1% in 1996. The recommended fluconazole dosage in Norway for the treatment of systemic candida infections is 400 mg on the first day and 200 mg per day thereafter (400 mg per day for serious infections). It is possible that a higher dosage should be used to ensure adequate treatment of patients with infections caused by less susceptible yeast isolates and possibly also to prevent the selection of such isolates.

In conclusion, this study has shown that the incidence of bloodstream fungal infections in Norway is remarkably low compared to that in the United States and that this low rate remained constant for a 6-year period from 1991 to 1996. The reason for this difference is not known, but it would be interesting to investigate if this could be explained by differences in antibiotic use patterns.

ACKNOWLEDGMENTS

We acknowledge the excellent technical assistance of Kari Nilsen and Ingrid Grønli.

REFERENCES

1. **Abi-Said, D., E. Anaissie, O. Uzun, I. Raad, H. Pinzcowski, and S. Vartivarian.** 1997. The epidemiology of hematogenous candidiasis caused by different *Candida* species. Clin. Infect. Dis. **24:**1122–1128.
2. **Andrew, M., and C. O. Solberg.** 1994. Use of antimicrobial agents in Norway 1980–92. Tidsskr. Nor. Laegeforen. **114:**169–173.
3. **Auger, P., C. Dumas, and J. Joly.** 1979. A study of 666 strains of Candida albicans: correlation between serotype and susceptibility to 5-fluorocytosine. J. Infect. Dis. **139:**590–594.
4. **Badenhorst, L., P. L. Botha, and M. N. van Rensburg.** 1991. The incidence of hospital fungal infections—yeast fungaemia. S. Afr. Med. J. **79:**302–303.
5. **Banerjee, S. N., T. G. Emori, D. H. Culver, R. P. Gaynes, W. R. Jarvis, T. Horan, J. R. Edwards, J. Tolson, T. Henderson, and W. J. Martone.** 1991. Secular trends in nosocomial primary bloodstream infections in the United States, 1980–1989. Am. J. Med. **91:**86S–89S.
6. **Beck Sague, C., and W. R. Jarvis.** 1993. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980–1990. J. Infect. Dis. **167:**1247–1251.
7. **Bruun, B., H. Westh, and J. Stenderup.** 1995. Fungemia: an increasing problem in a Danish university hospital 1989 to 1984. J. Clin. Microbiol. Infect. **1:**124–126.
8. **Chakrabarti, A., A. Ghosh, R. Batra, A. Kaushal, P. Roy, and H. Singh.** 1996. Antifungal susceptibility pattern of non-albicans Candida species & distribution of species isolated from candidaemia cases over a 5 year period. Indian J. Med. Res. **104:**171–176.
9. **Chen, Y. C., S. C. Chang, C. C. Sun, L. S. Yang, W. C. Hsieh, and K. T. Luh.** 1997. Secular trends in the epidemiology of nosocomial fungal infections at a teaching hospital in Taiwan, 1981 to 1993. Infect. Control Hosp. Epidemiol. **18:**369–375.
10. **Cockerill, F. R., III, J. G. Hughes, E. A. Vetter, R. A. Mueller, A. L. Weaver, D. M. Ilstrup, J. E. Rosenblatt, and W. R. Wilson.** 1997. 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. **24:**403–418.
11. **Colombo, A. L., M. Nucci, M. J. Caiuby, R. Salomao, M. L. Branchini, R. Richtnann, M. Ramalho, T. Perecmanis, and S. B. Wey.** 1996. High incidence of non-albicans candidemia despite rare use of azoles, abstr. J45, p. 226. *In* Program and abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
12. **Haug, J. B., S. Harthug, T. Kalager, A. Digranes, and C. O. Solberg.** 1994. Bloodstream infections at a Norwegian university hospital, 1974–1979 and 1988–1989: changing etiology, clinical features, and outcome. Clin. Infect. Dis. **19:**246–256.
13. **Horn, R., B. Wong, T. E. Kiehn, and D. Armstrong.** 1985. Fungemia in a cancer hospital: changing frequency, earlier onset, and results of therapy. Rev. Infect. Dis. **7:**646–655.
14. **Hung, C. C., Y. C. Chen, S. C. Chang, K. T. Luh, and W. C. Hsieh.** 1996. Nosocomial candidemia in a university hospital in Taiwan. J. Formos. Med. Assoc. **95:**19–28.
15. **Jarvis, W. R.** 1995. Epidemiology of nosocomial fungal infections, with emphasis on *Candida* species. Clin. Infect. Dis. **20:**1526–1530.
16. **Kennedy, M. J., and P. A. Volz.** 1985. Effect of various antibiotics on gastrointestinal colonization and dissemination by Candida albicans. Sabouraudia **23:**265–273.
17. **Nakazawa, S., T. Mori, I. Hibiya, and T. Oguri.** 1992. Analysis of 84 cases with fungemia. Kansenshogaku. Zasshi. **66:**612–619.
18. **National Committee for Clinical Laboratory Standards.** 1997. Reference method for broth dilution antifungal susceptibility testing of yeasts. Approved standard M-27A. National Committee for Clinical Laboratory Standards, Wayne, Pa.
19. **Nguyen, M. H., J. E. Peacock, Jr., A. J. Morris, D. C. Tanner, M. L. Nguyen, D. R. Snydman, M. M. Wagener, M. G. Rinaldi, and V. L. Yu.** 1996. The changing face of candidemia: emergence of non-Candida albicans species and antifungal resistance. Am. J. Med. **100:**617–623.

19a. **Norwegian Medicinal Depot.** Personal communication.

20. **Pfaller, M., and R. Wenzel.** 1992. Impact of the changing epidemiology of fungal infections in the 1990s. Eur. J. Clin. Microbiol. Infect. Dis. **11:**287–291.
21. **Pfaller, M. A., and A. L. Barry.** 1994. Evaluation of a novel colorimetric broth microdilution method for antifungal susceptibility testing of yeast isolates. J. Clin. Microbiol. **32:**1992–1996.
22. **Pfaller, M. A., J. H. Rex, and M. G. Rinaldi.** 1997. Antifungal susceptibility testing: technical advances and potential clinical applications. Clin. Infect. Dis. **24:**776–784.
23. **Pittet, D., and R. P. Wenzel.** 1995. Nosocomial bloodstream infections.

Secular trends in rates, mortality, and contribution to total hospital deaths. Arch. Intern. Med. **155:**1177–1184.
24. **Price, M. F., M. T. LaRocco, and L. O. Gentry.** 1994. Fluconazole susceptibilities of *Candida* species and distribution of species recovered from blood cultures over a 5-year period. Antimicrob. Agents Chemother. **38:**1422–1424.
25. **Radetsky, M., R. C. Wheeler, M. H. Roe, and J. K. Todd.** 1986. Microtiter broth dilution method for yeast susceptibility testing with validation by clinical outcome. J. Clin. Microbiol. **24:**600–606.
26. **Rex, J. H., M. A. Pfaller, J. N. Galgiani, M. S. Bartlett, A. Espinel-Ingroff, M. A. Ghannoum, M. Lancaster, F. C. Odds, M. G. Rinaldi, T. J. Walsh, and A. L. Barry.** 1997. Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of in vitro-in vivo correlation data for fluconazole, itraconazole, and Candida infections. Clin. Infect. Dis. **24:**235–247.
27. **Rotstein, C., D. Yamamura, and L. Nicolle.** 1996. Candidemia in Canada 1992–94, abstr. J41, p. 226. *In* Program and abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, D.C.
28. **Samonis, G., A. Gikas, E. J. Anaissie, G. Vrenzos, S. Maraki, Y. Tselentis, and G. P. Bodey.** 1993. Prospective evaluation of effects of broad-spectrum antibiotics on gastrointestinal yeast colonization of humans. Antimicrob. Agents Chemother. **37:**51–53.
29. **Sandven, P.** 1990. Laboratory identification and sensitivity testing of yeast isolates. Acta Odontol. Scand. **48:**27–36.
30. **Sandven, P.** 1997. Multicountry candidemia survey. Clin. Microbiol. Infect. **3**(Suppl. 2)**:**15.
31. **Sandven, P., A. Bjorneklett, and A. Maeland.** 1993. Susceptibilities of Norwegian *Candida albicans* strains to fluconazole: emergence of resistance. Antimicrob. Agents Chemother. **37:**2443–2448.
32. **Stiller, R. L., J. E. Bennett, H. J. Scholer, M. Wall, A. Polak, and D. A. Stevens.** 1982. Susceptibility of 5-fluorocytosine and prevalence of serotype in 402 *Candida albicans* isolates from the United States. Antimicrob. Agents Chemother. **22:**482–487.
33. **Voss, A., J. A. Kluytmans, J. G. Koeleman, L. Spanjaard, C. M. Vandenbroucke Grauls, H. A. Verbrugh, M. C. Vos, A. Y. Weersink, J. A. Hoogkamp Korstanje, and J. F. Meis.** 1996. Occurrence of yeast bloodstream infections between 1987 and 1995 in five Dutch university hospitals. Eur. J. Clin. Microbiol. Infect. Dis. **15:**909–912.
34. **Wenzel, R. P.** 1995. Nosocomial candidemia: risk factors and attributable mortality. Clin. Infect. Dis. **20:**1531–1534.
35. **White, M. H.** 1997. The contribution of fluconazole to the changing epidemiology of invasive candidal infections. Clin. Infect. Dis. **24:**1129–1130.
36. **Wingard, J. R., W. G. Merz, M. G. Rinaldi, T. R. Johnson, J. E. Karp, and R. Saral.** 1991. Increase in Candida krusei infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. N. Engl. J. Med. **325:**1274–1277.