MAJOR ARTICLE

Epidemiology of Candidemia in Swiss Tertiary Care Hospitals: Secular Trends, 1991–2000

Oscar Marchetti,[1] Jacques Bille,[2] Ursula Fluckiger,[3] Philippe Eggimann,[4] Christian Ruef,[5] Jorge Garbino,[6] Thierry Calandra,[1] Michel-Pierre Glauser,[1] Martin George Täuber,[7] and Didier Pittet,[4] for the Fungal Infection Network of Switzerland (FUNGINOS)[a]

[1]Infectious Diseases Service, Department of Internal Medicine, and [2]Institute of Microbiology, Centre Hospitalier Universitaire Vaudois, Lausanne, [3]Division of Infectious Diseases, Department of Internal Medicine, Kantonsspital, Basel, [4]Infection Control Program and [6]Division of Infectious Diseases, Department of Internal Medicine, University of Geneva Hospitals, Geneva, [5]Division of Infectious Diseases and Hospital Epidemiology, Department of Internal Medicine, Universitätsspital, Zürich, and [7]Institute of Infectious Diseases, Inselspital, Bern, Switzerland

Candida **species are among the most common bloodstream pathogens in the United States, where the emergence of azole-resistant *Candida glabrata* and *Candida krusei* are major concerns. Recent comprehensive longitudinal data from Europe are lacking. We conducted a nationwide survey of candidemia during 1991–2000 in 17 university and university-affiliated hospitals representing 79% of all tertiary care hospital beds in Switzerland. The number of transplantations and bloodstream infections increased significantly ($P < .001$). A total of 1137 episodes of candidemia were observed: *Candida* species ranked seventh among etiologic agents (2.9% of all bloodstream isolates). The incidence of candidemia was stable over a 10-year period. *C. albicans* remained the predominant *Candida* species recovered (66%), followed by *C. glabrata* (15%). *Candida tropicalis* emerged (9%), the incidence of *Candida parapsilosis* decreased (1%), and recovery of *C. krusei* remained rare (2%). Fluconazole consumption increased significantly ($P < .001$). Despite increasing high-risk activities, the incidence of candidemia remained unchanged, and no shift to resistant species occurred.**

Candida species are the most important causes of nosocomial fungal infection, a major challenge of modern medicine. Paradoxically, medical progress associated with an ever-growing number of invasive procedures, increasingly aggressive immunosuppressive treatments, and widespread use of broad-spectrum antibiotics is the main contributor to this occurrence. Candidemia is associated with high morbidity, prolonged hospital stay, high attributable mortality (~40%), and substantial health care costs [1–4].

The epidemiology of candidemia has been extensively studied in the United States. Secular trends among hospitals reporting to the National Nosocomial Infections Surveillance (NNIS) system showed a clear-cut association between the incidence of candidemia and the number of hospital beds and/or academic affiliation [5]. *Candida* species were the fourth most commonly isolated pathogens in patients with bloodstream infections and accounted for 10% of all such infections in the 1990s [4, 6, 7]. An inverse trend in the late 1990s among patients in intensive care units (ICUs) was reported by Trick et al. [8]. Although *Candida albicans* has been the predominant species for several decades, a substantial shift to dose-dependent azole-susceptible or even intrinsically azole-resistant non-*albicans* species of *Candida,* such as *Candida glabrata* and *Candida krusei,* was observed more recently in many US hospitals [9, 10]. Infections due to these non-*albicans* species are causes

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[a] Participating hospitals and affiliated microbiology laboratories are listed at the end of the text.

Reprints or correspondence: Dr. Oscar Marchetti, Infectious Diseases Service, Dept. of Internal Medicine, Centre Hospitalier Universitaire Vaudois, CH-1011 Lausanne, Switzerland (Oscar.Marchetti@chuv.hospvd.ch).

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of increased morbidity and mortality [11]. Several studies have attributed these epidemiologic changes to the increased use of azole prophylaxis, but this remains a subject of debate [12].

Few comprehensive epidemiological data are available from European hospitals [13, 14]. Dutch investigators reported a 2-fold increase in the incidence of candidemia, with a shift toward non-*albicans* species of *Candida* in university hospitals in the early 1990s [13]. In contrast, a Norwegian survey conducted during the same period described a stable incidence of candidemia and a stable distribution of *Candida* species [15]. A study from the Invasive Fungal Infections Group of the European Organization for the Research and Treatment of Cancer reported that *C. glabrata* and *C. krusei* were recovered from higher proportions of patients with cancer who received azole prophylaxis than from those who did not [11]. A laboratory-based investigation conducted by the European Confederation of Clinical Mycology (ECCM) in 1998–1999 showed the predominance of *C. albicans*.

These observations suggest that the epidemiology of candidemia in Europe might differ from that in the United States. However, to our knowledge, no recent longitudinal multicenter study has been performed in Europe. We conducted a nationwide survey of Swiss tertiary care hospitals to study the secular trends in patient-care activities and hospital characteristics associated with the epidemiology of candidemia during 1991–2000.

METHODS

Participating hospitals. All Swiss university hospitals (5 health care centers and 2 independent pediatric hospitals) and a representative sample of university-affiliated tertiary care teaching centers ($n = 11$) were included in a retrospective survey. These institutions are distributed across the country and play a key role in the national health care system by serving the majority of the population of Switzerland (~6,100,000 [84%] of 7,200,000 residents). All hematopoietic stem cell and solid-organ transplantations are performed in these centers, where infectious diseases specialists are in charge of prevention, control, and management of infections.

Study variables. The following variables were recorded by questionnaire survey: hospital characteristics in 2000 (type of hospital; number of beds; number of patient admissions; and patient-days spent in the medical, surgical, and pediatric wards and ICUs); high-risk activities for invasive fungal infection in 2000 (the number of cases of acute leukemia and hematopoietic stem cell and solid-organ transplantations); clinical and/or teaching activities and resources associated with the management of infectious diseases and infection-control programs in 2000; laboratory methods used for the diagnosis of candidemia (see below); episodes of candidemia during 1991–2000 (number of isolates of each species; number of isolates tested and found to be resistant to fluconazole, amphotericin B, or 5-flucytosine; and patient location in the hospital at the time of candidemia). The questionnaire was distributed to reference infectious diseases specialist(s) and clinical microbiologist(s) at each participating hospital. Returned questionnaires (from 17 of the 18 hospitals) were checked by the survey coordinators for completeness and consistency. Those with missing data or inconsistencies were returned for completion and/or correction.

Data on the number of patient-days spent in the hospital, the transplantation activities, the number of blood cultures performed, the 10 most frequently recovered bloodstream isolates, and the consumption of fluconazole during 1991–2000 were additionally obtained from a representative sample of university and university-affiliated hospitals. General data on the characteristics of Swiss hospitals were obtained from the Swiss Federal Office for Statistics (http://www.statistique.admin.ch).

Participating microbiology laboratories. Sixteen microbiology laboratories are affiliated with the 17 participating hospitals. All laboratories used automated blood culture systems (12 used Bactec [Becton Dickinson] and 5 used BacT/Alert [bioMérieux]), and 7 (44%) of 16 used special blood culture bottles for fungus detection (5 used Bactec Mycosis IC/F vials [Becton Dickinson] and 2 used other types). Recognized standard laboratory techniques for *Candida* species identification were used by all laboratories [16]. Identification of *Candida* bloodstream isolates was systematically performed by 12 (75%) of 16 laboratories; 3 (19%) of 16 laboratories submitted strains for identification to a referral laboratory. Antifungal susceptibility testing, the quality control of which was based on NCCLS recommendations, was performed in 7 (44%) of 16 laboratories [17]. In 2000, 8 (50%) of 16 institutions sent selected strains to a referral laboratory for antifungal susceptibility testing.

Statistical analysis. Continuous variables were compared using Student's t test or the Mann-Whitney U test, as appropriate. Proportions were compared using the χ^2 test or Fisher's exact test, as appropriate. Linear trends over time were analyzed by nonparametric Spearman rank order correlation analysis, using years as the independent variable. All P values were based on 2-tailed tests of significance ($P < .05$). Statistical analysis was performed using SPSS software, version 11.0 (SPSS).

RESULTS

Hospital characteristics and patient-care activities. The number of beds, administrative data, and high-risk patient-care activities of the 17 participating institutions in 2000 are summarized in table 1. A total of 9333 beds representing 79% of all tertiary care hospital beds in Switzerland were included in the survey; 56% of the beds were in 7 university hospitals, and 44% were in 10 university-affiliated institutions. The median number of beds was higher among university hospitals (977

Table 1. Characteristics and activities of 17 surveyed Swiss tertiary care hospitals, 2000.

Characteristic	Hospital type		
	University	University affiliated	All
Hospital size, no. of beds[a]			
100–249 beds	2 (117–120)[b]	3 (209–242)	5 (117–242)
250–499 beds	…	3 (250–402)	3 (250–402)
500–749 beds	…	4 (502–704)	4 (502–704)
750–1000 beds	3 (855–977)	…	3 (855–977)
>1000 beds	2 (1022–1200)	…	2 (1022–1200)
Total no. of beds[c]	5186	4147	9333
No. of patient admissions[c]	196,006 (5400–44,599)	142,060 (8534–24,506)	338,066 (5400–44,599)
Patient-days, by ward[c]			
Medicine	469,668 (55,026–136,985)	422,440 (21,333–64,986)	892,118 (21,333–136,985)
Surgery	456,776 (74,499–110,282)	427,171 (15,890–81,940)	883,947 (15,890–110,282)
Pediatrics	163,903 (17,283–49,644)[d]	81,081 (2645–25,852)	244,984 (2645–49,644)
ICU	93,798 (8150–20,511)[d]	47,318 (1741–9177)	141,116 (1741–20,511)
Total	1,184,155 (44,150–316,749)	978,010 (43,769–181,795)	2,162,165 (43,769–316,749)
Occupancy rate, median % (range)	86 (74–96)	85 (72–93)	85.5 (72–96)
Acute leukemia, no. of patients	179[e]	73	252
Type of transplantation, no. performed			
Solid organ	400[e,f]	21[g]	421
Allogeneic HSC	110[e]	…	110
Autologous HSC	215[e]	44	259
Total	725[e]	65	790

NOTE. HSC, hematopoietic stem cell; ICU, intensive care unit.

[a] Data are no. of hospitals (range of no. of beds for individual hospitals).

[b] Both are independent pediatric university hospitals.

[c] Data are total values for all surveyed hospitals.

[d] $P < .001$ for proportions of pediatric and ICU patient-days over total patient-days in university versus university-affiliated hospitals.

[e] $P < .001$ for university vs. university-affiliated hospitals.

[f] Includes kidney (248 transplantations), liver (77), heart (38), lung-heart (24), and pancreas (13).

[g] All were kidney transplantations.

beds [range, 855–1200 beds], not including the 2 independent pediatric hospitals) than among university-affiliated hospitals (380 beds; range, 209–704 beds; $P < .05$). In 2000, 338,066 admissions and 2,162,165 patient-days were reported by the participating institutions. Significantly more patient-days were reported by university hospitals than by university-affiliated hospitals ($P < .05$). ICUs accounted for 7.9% of patient-days in university hospitals, compared with 4.8% of patient-days in university-affiliated institutions ($P < .001$).

All surveyed hospitals had clinical and teaching activities associated with infectious diseases. All university hospitals—with the exception of 1 independent pediatric center—and 6 (60%) of 10 university-affiliated hospitals had an infection-control program (85% used the Centers for Disease Control and Prevention definitions for nosocomial infections).

In 2000, most cases of acute leukemia (71%) and transplantations (92%) were reported by university hospitals. In 3 university hospitals, hematopoietic stem cell transplantations increased 124%, from 55 in 1992 to 123 in 2000 ($r = 0.83$; $P < .005$), and solid-organ transplantations increased 95% during the same period, from 108 to 211 ($r = 0.95$; $P < .001$) (figure 1*A*).

Patient location in the hospital and the incidence of candidemia. Data on the hospital ward distribution of 92 (77%) of all 117 patients with candidemia reported in 2000 were available from 10 hospitals. The overall incidence of infection was 0.49 cases per 10,000 patient-days. When university ($n = 5$) and university-affiliated hospitals ($n = 5$) were compared, the incidence of candidemia was higher in the former, but the difference did not reach statistical significance ($P = .17$). The incidence of candidemia varied according to patient location in the hospital (table 2). Overall, candidemia occurred 7 times more frequently in ICUs than in other wards ($P = .11$). This difference reached statistical significance in university hospitals ($P < .01$).

Information from 3 university hospitals and 2 university-affiliated hospitals on patient location in the hospital at the time of candidemia was available for 664 episodes during 1991–2000 (figure 2). A comparison of the periods 1991–1995 and 1996–2000 showed that 109 (32%) of 355 and 107 (35%) of

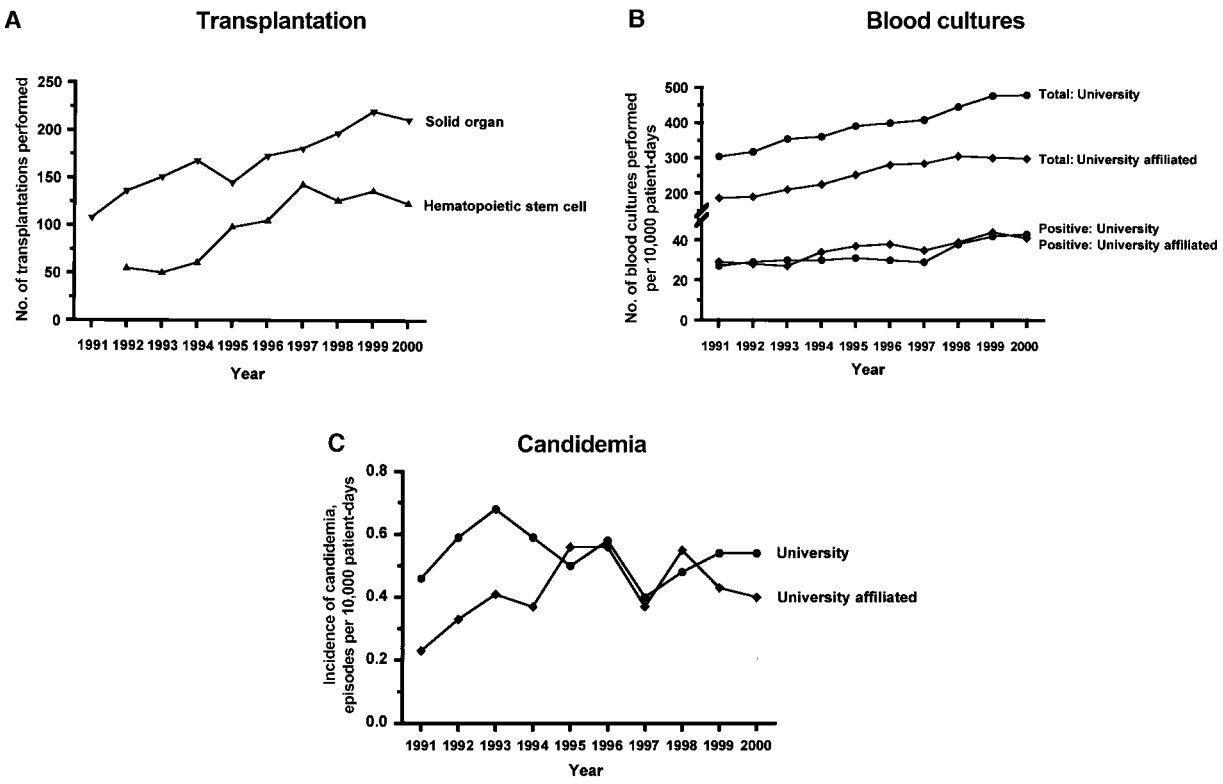

Figure 1. *A,* Transplantation activity in 3 university hospitals during 1991–2000. The increase over time is statistically significant for hematopoietic stem cell transplantations ($r = 0.83$; $P < .005$) and solid-organ transplantations ($r = 0.95$; $P < .001$). *B,* Blood cultures performed in 3 university and 3 university-affiliated hospitals during 1991–2000. The total number of blood cultures per 10,000 patient-days per year increased significantly ($r = 1.0$ in university hospitals [$P < .001$] and $r = 0.95$ in university-affiliated hospitals [$P < .001$]). Similar trends were observed for the number of positive blood culture results (i.e., growth of any pathogen) ($r = 0.81$ in university hospitals [$P < .001$] and $r = 0.90$ in university-affiliated hospitals [$P < .001$]). *C,* Incidence of candidemia in 3 university and 3 university-affiliated hospitals during 1991–2000. No significant trend was found during the 10-year period. However, during 1991–1996, the incidence increased significantly ($r = 0.90$; $P < .05$) in university-affiliated hospitals.

309 of all episodes, respectively, occurred in patients in ICUs. The proportion of isolates recovered from patients in medical wards (including hemato-oncology units) and medical ICUs increased from 25% to 31% ($P = .06$) and from 10% to 15% ($P = .06$), respectively. In contrast, the proportion of isolates recovered from patients in pediatric wards decreased from 22 (6%) of 355 to 6 (2%) of 309 ($P < .01$). The proportions of *Candida* isolates recovered from patients in other hospital sectors did not significantly differ over time. No significant difference was observed between university and university-affiliated institutions.

Candidemia trends during 1991–2000. Data on the number of positive blood culture results and the incidence of candidemia during 1991–2000 were available for 3 university hospitals and 3 university-affiliated hospitals. In these institutions, 533,490 blood cultures were performed over a 10-year period. Of these, 52,565 (9.8%) were positive (i.e., cultures yielded any pathogen). As shown in figure 1*B*, the total number of blood cultures performed per 10,000 patient-days increased from 304 in 1991 to 479 in 2000 in university hospitals ($r = 1.0$; $P < .001$) and from 186 to 299 during the same period in university-affiliated hospitals ($r = 0.95$; $P < .001$). Similar trends were observed for the annual number of positive blood culture results (i.e., cultures yielded any pathogen), which increased from 27 to 43 ($r = 0.81$; $P < .001$) and 29 to 41 positive blood culture results per 10,000 patient-days ($r = 0.90$; $P < .001$), respectively (figure 1*B*).

In the surveyed hospitals, *Candida* species accounted for 2.9% of the bloodstream pathogens (median annual proportion, 2.8%; range, 2.3%–3.4%) and ranked seventh (median annual rank, eighth; range, sixth to ninth) behind coagulase-negative staphylococci (20.2%), *Escherichia coli* (19.4%), *Staphylococcus aureus* (12.7%), *Streptococcus pneumoniae* (6.7%), other streptococci (4.7%), and *Klebsiella* species (3.9%) and ahead of enterococci (2.6%), *Pseudomonas aeruginosa* (2.6%), and anaerobes (1.4%). No significant difference was observed between university and university-affiliated hospitals.

These 6 centers reported 774 (68%) of all 1137 episodes of candidemia recorded in the survey over 10 years. The median incidence of candidemia was 0.50 episodes per 10,000 patient-

Table 2. Data on the number of episodes and the incidences of candidemia in 2000, according to patient location in the hospital, reported by 17 surveyed Swiss tertiary care hospitals.

	Hospital type					
	University		University affiliated		All	
Patient location	No. of episodes	Incidence[a]	No. of episodes	Incidence[a]	No. of episodes	Incidence[a]
Ward	45	0.47 (0.16–0.64) [b]	13	0.16 (0.06–0.57)	58	0.33 (0.06–0.64) [c]
Medical[d]	25	0.51 (0.25–1.19)[e,f]	5	0.15 (0–0.47)	30	0.39 (0–1.19)
Surgical	14	0.23 (0.09–0.64)[g]	6	0 (0–1.03)	20	0.27 (0–1.03)
Pediatric	0	0	0	0	0	0
ICU	23	1.9 (0.91–6.7)	7	0 (0–9.36)	30	2.36 (0–9.36)
Medical	9	2.5 (1.67–13.3)[h]	3	0 (0–12.3)	12	3.33 (0–13.3)
Surgical	13	2.86 (0–12)	4	0 (0–12.5)	17	3.27 (0–12.5)
Pediatric[i]	1	0 (0–0.5)	0	0	1	0.26 (0–0.5)
Overall	70[j]	0.57 (0.44–1.04)[k]	22[j]	0.35 (0.06–1.14)	92[l]	0.49 (0.06–1.14)

NOTE. ICU, intensive care unit.

[a] Data are median no. of episodes per 10,000 patient-days (range).
[b] $P < .01$ versus ICUs in university hospitals.
[c] $P = .11$ versus ICUs in all hospitals.
[d] Includes oncohematology units.
[e] $P < .05$ versus medical wards in university-affiliated hospitals.
[f] $P < .01$ versus medical ICUs in university hospitals.
[g] $P = .11$ versus surgical ICUs in university hospitals.
[h] $P = .14$ versus medical ICUs in university-affiliated hospitals.
[i] Includes neonatal ICUs.
[j] Hospital location of 2 patients is unknown.
[k] $P = .17$ versus university-affiliated hospitals.
[l] Hospital location of 4 patients is unknown.

days per year (range, 0.38–0.58 episodes per 10,000 patient-days per year). No significant trend was observed during the 10-year period among university hospitals and university-affiliated hospitals (figure 1*C*). It is notable, however, that the annual incidence of candidemia in university-affiliated hospitals increased significantly, from 0.23 to 0.56 episodes per 10,000 patient-days ($r = 0.93$; $P < .05$), during 1991–1996.

Candida *species distribution during 1991–2000.* Data on 1137 candidemia episodes were available for the period 1991–2000 from all participating hospitals. Overall, the species distribution was stable (figure 3). *C. albicans* remained the predominant species, ranging between 64% and 68% of all isolates recovered, and *C. glabrata* was the second most common species recovered (14% during 1991–1993 and 15% during 2000). *C. tropicalis* emerged as the third most common pathogen (2% during 1991–1993 and 9% during 2000; $P < .005$), whereas the incidence of *C. parapsilosis* decreased (6% during 1991–1993 and 1% during 2000; $P < .05$). *C. krusei* remained rare (2% during 1991–1993 and 2% during 2000). During the 10-year study period, the overall proportion of non-*albicans* species of *Candida* was 36% in university hospitals and 31% in university-affiliated hospitals ($P = .18$). *C. glabrata* accounted for 15.5% and 10% of isolates, respectively ($P < .05$).

Secular trends of the incidence of candidemia caused by different *Candida* species were available from 3 university hospitals and 3 university-affiliated hospitals (774 isolates; figure 4*A*). Although the annual incidence varied over time for *C. albicans* (median, 0.34 episodes per 10,000 patient-days; range, 0.26–0.38 episodes per 10,000 patient-days), *C. glabrata* plus *C. krusei* (median, 0.075 episodes per 10,000 patient-days; range, 0.04–0.12 episodes per 10,000 patient-days), and other non-*albicans Candida* species (median, 0.085 episodes per 10,000 patient-days; range, 0.04–0.13 episodes per 10,000 patient-days), no statistically significant trend was observed. Similarly, no trend was observed when university and university-affiliated hospitals were analyzed separately.

Fluconazole administration. The annual quantity of fluconazole administered in 1991–2000 in these 3 university and 3 university-affiliated hospitals is illustrated in figure 4*B*. A progressive increase in the quantities of the parenteral and oral forms that were administered was observed. In 1991, 2.1 and 5.2 g per 10,000 patient-days were administered intravenously and orally, respectively; in 2000, 12.2 and 17.8 g per 10,000 patient-days were administered, respectively ($r = 0.99$ [$P < .001$] and $r = 0.97$ [$P < .001$], respectively). Identical trends were observed when university and university-affiliated hospitals were analyzed separately.

Antifungal susceptibility testing. In 1999–2000, data on fluconazole susceptibility were available for 96 (39%) of 245 *Candida* isolates, comprising 90 (60%) of 151 isolates from

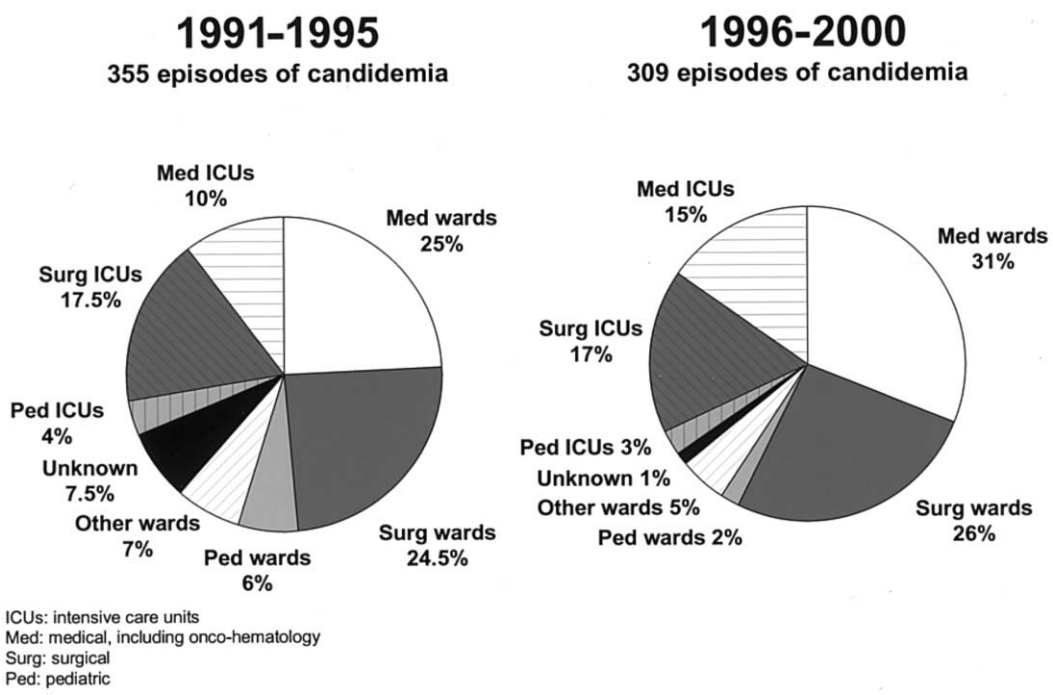

Figure 2. Patient location in the hospital at time of candidemia in 3 university and 2 university-affiliated tertiary care institutions during 1991–1995 and 1996–2000. The following differences or trends were observed in a comparison of both periods: pediatric wards, $P < .01$; medical wards, $P = .06$; and medical ICUs, $P = .06$. Pediatric ICUs include neonatal ICUs.

university hospitals and 6 (6%) of 94 from university-affiliated hospitals ($P < .001$). Fifty-six *C. albicans* isolates and 40 non-*albicans* isolates of *Candida* were tested for susceptibility to fluconazole, and 1 (2%) and 8 (20%) of the isolates, respectively, were resistant, according to the NCCLS criteria. Resistant non-*albicans* isolates of *Candida* included 5 *C. glabrata* isolates, 1 *C. krusei* isolate, 1 *Candida norvegiensis* isolate, and 1 *C. tropicalis* isolate. During 1997–1998, a similar proportion of fluconazole-resistant non-*albicans* isolates of *Candida* was reported (5 [24%] of 21 isolates, of which 4 were *C. glabrata* and 1 was *C. krusei*), suggesting that the rate of azole resistance did not increase during 1997–2000. No resistance to amphotericin B and 5-flucytosine was observed in 1999–2000 in 35 and 29 *Candida* isolates, respectively. Because antifungal susceptibility testing became common practice only during the late 1990s, data on 10-year trends are not available.

DISCUSSION

We conducted a comprehensive analysis of trends of candidemia, hospital characteristics, activities at-risk for *Candida* infections, and fluconazole use in Swiss tertiary care hospitals during 1991–2000. *Candida* species ranked among the top 10 bloodstream pathogens that were recovered during the study period, but no change in the incidence of candidemia occurred, despite an increasing number of high-risk clinical settings. Although fluconazole use increased significantly over the 10-year period, no shift toward azole-resistant non-*albicans* species of *Candida* and no resistance in *C. albicans* were observed.

Invasive candidiasis emerged as a major problem in US hospitals in the 1980s [5, 7]. A similar evolution was observed in Asia [18]. However, an inverse trend was observed during 1989–1999 among ICUs in US hospitals reporting to the NNIS system [8]. In Europe, contrasting data were reported in the early 1990s—the incidence of candidemia increased in The Netherlands and remained stable in Norway [13, 15]. No significant change was reported in 1 Swiss hospital between 1989 and 2000 [19]. Other recent multicenter longitudinal data from Europe are lacking.

We studied the epidemiology of candidemia over a 10-year period in all university hospitals and the majority of university-affiliated tertiary care centers, serving >80% of the population of Switzerland. The analysis of hospital characteristics and activities shows a significant increase in the number of blood cultures and transplantations performed, representing an increased number of clinical settings at high risk for candidemia. *Candida* organisms ranged from the sixth through ninth most recovered bloodstream pathogens and accounted for 2%–3% of all isolates during this period. These data are comparable to those reported from other European countries. In contrast,

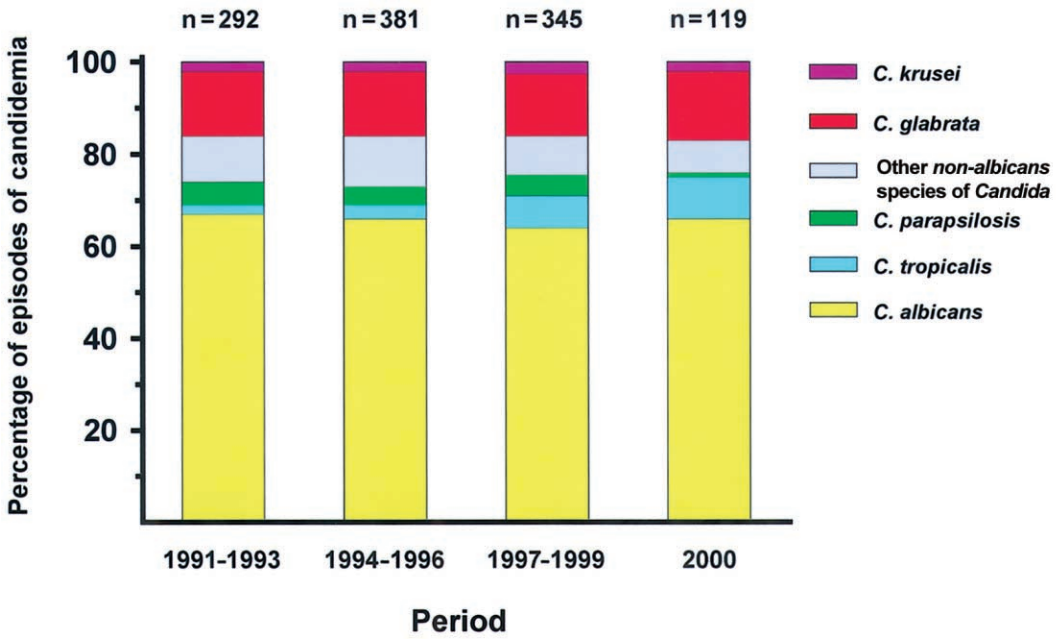

Figure 3. Evolution of the distribution of *Candida* species in all surveyed hospitals during 1991–2000. The proportion of *Candida tropicalis* increased from 2% to 9% ($P < .005$) and that of *Candida parapsilosis* decreased from 6% to 1% ($P < .05$). For the other *Candida* species, no significant change was observed.

Candida species ranged from the fourth to fifth most recovered bloodstream isolates and accounted for 7%–10% of all infections in the United States.

In Switzerland, the incidence of candidemia remained essentially unchanged during the 10-year study period. In 2000, 0.54 episodes per 10,000 patient-days (0.36 episodes per 1000 hospital admissions) and 0.40 episodes per 10,000 patient-days (0.15 episodes per 1000 hospital admissions) were reported in university and university-affiliated hospitals, respectively. In 1989, the NNIS system described 2- to 3-fold higher rates—0.61 and 0.37 episodes per 1000 discharges in large (>500-bed) and small (<500-bed) US teaching hospitals, respectively [5]. Ten years later, Berrouane et al. [20] observed 0.98 episodes of candidemia per 10,000 patient-days in 1 US tertiary care center. The following incidence rates reported in European countries in the 1990s were closer to those found in Switzerland: 0.72 episodes per 10,000 patient-days in Dutch university hospitals, 0.52 episodes per 10,000 patient-days (0.38 episodes per 1000 admissions) in French teaching hospitals, 0.44 episodes per 10,000 patient-days (0.38 episodes per 1000 admissions) in Italian hospitals, and 0.37 episodes per 10,000 patient-days in Norwegian university hospitals [13, 15, 21, 22].

Critically ill and severely immunocompromised patients are at particularly high risk for invasive candidiasis. In Switzerland, one-third of all episodes of candidemia occurred in ICUs, one-third in medical wards (including hemato-oncology units), and one-fourth in surgical wards. These proportions are comparable with those described in US hospitals [6, 20]. In 2000, we observed a 7-fold higher incidence of candidemia in ICUs (2.36 episodes per 10,000 patient-days) than in wards (0.33 episodes per 10,000 patient-days). In NNIS system hospitals, the incidence of candidemia in ICUs dropped from 5 to 2 episodes per 10,000 patient-days between 1991 and 1999 [8]. No comparative data in this clinical setting are available from other European countries.

The distribution of *Candida* species plays a key role for establishing efficient management strategies [23, 24]. The emergence of *Candida* species with decreased susceptibility or intrinsic resistance to azoles was a major concern in the 1990s. This phenomenon was first reported in the United States in neutropenic recipients of bone marrow transplants [9]. Other North American and European investigators confirmed these observations in larger hospital settings [10, 11, 13, 20, 22, 25, 26]. Trick et al. [8] recently confirmed these trends in patients in US ICUs. In institutions where this shift occurred, proportions of *C. glabrata* and *C. krusei* were 15%–45% and 5%–20%, respectively. However, this phenomenon was not described in other studies from Canada, Latin America, and Europe [15, 27]. In Switzerland, no shift to azole-resistant *Candida* species was observed over a 10-year period. *C. albicans* remained the predominant species, followed by *C. glabrata; C. tropicalis* emerged as the third most common species, the frequency of *C. parapsilosis* decreased, and *C. krusei* remained uncommon. The species distributions were very close to those reported in Norway

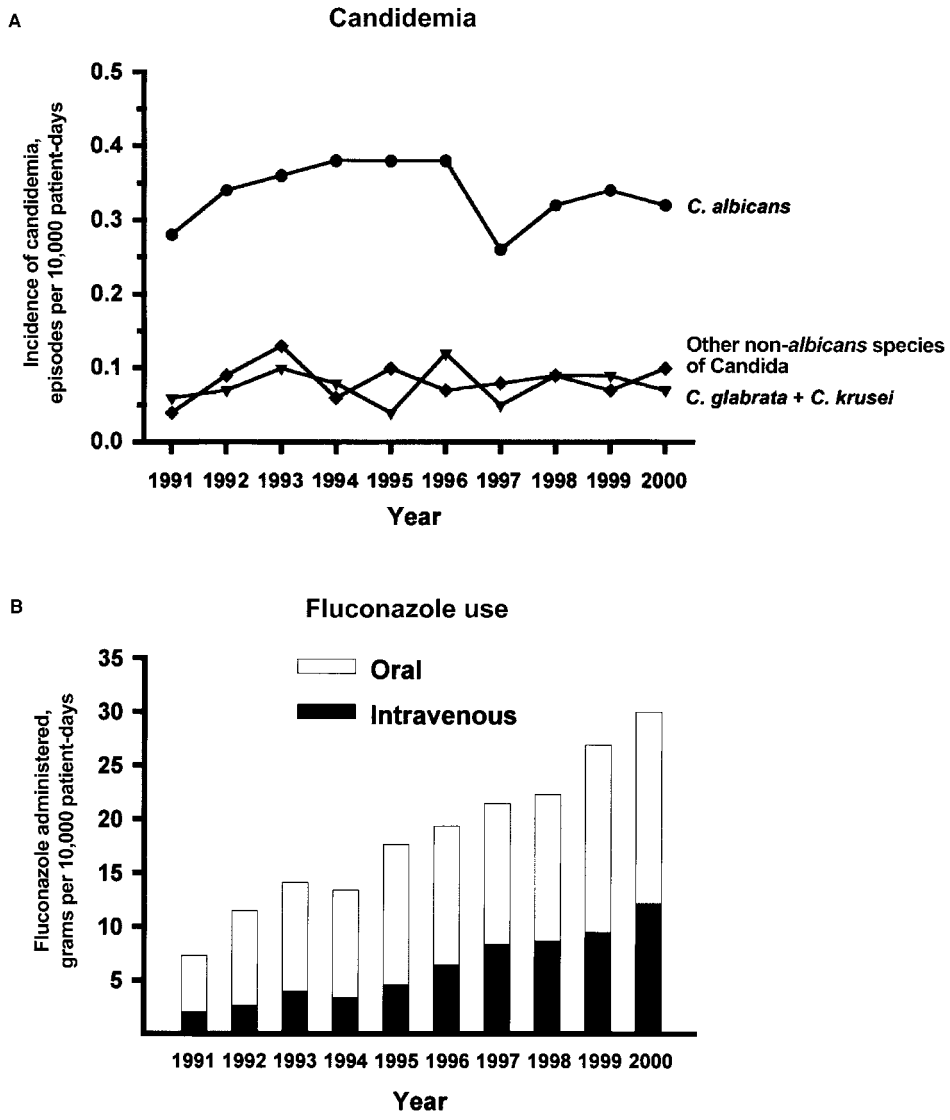

Figure 4. *A,* Incidence of candidemia due to different *Candida* species in 3 university and 3 university-affiliated hospitals during 1991–2000. No statistically significant trend was observed. *B,* Use of fluconazole in 3 university and 3 university-affiliated hospitals during 1991–2000. A statistically significant increase was found for the intravenous ($r = 0.99$; $P < .001$) and oral form ($r = 0.97$; $P < .001$).

during the early 1990s, in Italy during an ECCM survey conducted in the late 1990s, and in Wales [15, 22, 28].

The role of the widespread use of azoles in the shift to resistant *Candida* species has been largely debated and remains controversial [12]. Two groups observed an important increase of *C. glabrata* fungemia in the 1990s and analyzed fluconazole consumption over time. Voss et al. [13] evaluated the annual nationwide fluconazole use in The Netherlands in kilograms and observed a 4-fold increase between 1990 and 1995. Similarly, Berrouane et al. [20] observed a substantial increase in fluconazole use, from 3 to 33 g per 10,000 patient-days in 1990 and 1994, respectively. In contrast, a study from 1 Swiss university hospital reported no shift to non-*albicans* species of *Candida,* despite a significant increase in fluconazole use between 1989 and 2000 [19]. In the current study, the use of fluconazole in 6 university and university-affiliated hospitals increased 4-fold, from 7.3 to 30 g per 10,000 patient-days in 1991 and 2000, respectively. The association between the progressive rise in fluconazole use and the constant incidence of candidemia suggests that prophylactic and preemptive and/or empirical strategies in high-risk clinical settings might have played a role in stabilizing the incidence of the disease [29–31]. On the other hand, improved infection-control practices might have contributed to such stabilization, despite an increase of high-risk patient-care activities. The increased use of fluconazole did not influence the distribution of the different *Candida* species during the 10-year period under study.

Despite the lack of a centralized laboratory, this retrospective

study represents the largest European series of candidemia and one of the largest worldwide. It provides a longitudinal overview of the secular trends associated with patient-care activities, which is representative of the entire country over a 10-year period. The incidence of candidemia remained stable, despite increasing high-risk activities, and no shift to azole-resistant *Candida* species was observed. However, a prospective survey is needed to detect the possible emergence of resistance associated with a sustained use of azole antifungals.

FUNGAL INFECTION NETWORK OF SWITZERLAND

Participating hospitals and affiliated microbiology laboratories of the Fungal Infection Network of Switzerland (responsible infectious disease specialist(s); responsible clinical microbiologist): Kantonsspital, Aarau (T. Bregenzer; I. Heinzer); Kantonsspital, Basel (U. Fluckiger; R. Frei); Universitätskinderspital, Basel (U. Heininger; R. Hertel); Inselspital, Bern (M. Täuber; K. Mühlethaler); Kantonsspital, Chur (F. Fleisch; K. Eschmann); Hôpital Cantonal, Fribourg (C. Chuard; D. Frascheboud); Hôpitaux Universitaires, Genève (P. Eggimann, J. Garbino, and D. Pittet; P. Rohner); Hôpital Communal, La-Chaux-de-Fonds (D. Genné; R. Lienhard); Centre Hospitalier Universitaire Vaudois, Lausanne (T. Calandra, M.P. Glauser, and O. Marchetti; J. Bille); Kantonsspital, Liestal (W. Zimmerli; S. Graf); Ospedale Civico, Lugano (E. Bernasconi; M. Dolina); Kantonsspital, Luzern (M. Rossi; T. Rutz); Hôpital des Cadolles, Neuchâtel (R. Malinverni; R. Lienhard); Kantonsspital, St. Gallen (K. Boggian; D. Buhl); Universitätsspital, Zürich (C. Ruef; G. Schär); Universitätskinderspital, Zürich (D. Nadal and C. Berger [infectious diseases specialists]); Stadtspital Triemli, Zürich (J. Gubler [infectious diseases specialist]).

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