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# Occurrence of Yeast Bloodstream Infections between 1987 and 1995 in Five Dutch University Hospitals

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The aim of this study was to identify retrospectively trends in fungal bloodstream infections in The Netherlands in the period from 1987 to 1995. Results of over 395,000 blood cultures from five Dutch university hospitals were evaluated. Overall, there were more than 12 million patient days of care during the nine-year study period. The rate of candidemia doubled in the study period, reaching an incidence of 0.71 episodes per 10,000 patient days in 1995. The general increase in candidemia was paralleled by an increase in non-*Candida albicans* bloodstream infections, mainly due to *Candida glabrata*. However, more than 60% of the infections were caused by *Candida albicans*. Fluconazole-resistant species such as *Candida krusei* did not emerge during the study period. The increasing rate of candidemia found in Dutch university hospitals is similar to the trend observed in the USA, but the rate is lower and the increase is less pronounced.

In recent years, *Candida* species, most notably *Candida albicans*, have emerged as important nosocomial pathogens. Over the past decade, the incidence of *Candida* bloodstream infections increased two- to fivefold in teaching hospitals and one- to fourfold in non-teaching hospitals in the USA (1–3). Candidemia occurs most frequently in high-risk patients, such as immunocompromised patients with an underlying malignancy or hematological disorder (4, 5), severely ill burn-patients, and surgical and neonatal intensive care patients (5–10). Therefore, the incidence of candidemia is highest in tertiary care referral hospitals, with an incidence of 5–10 per 10,000 admissions (1). Nosocomial candidemia now accounts for 10–15% of all hospital-acquired bloodstream infections in hospitals in the USA, *Candida* thus being among the four predominant microorganisms causing nosocomial bloodstream infections (1, 11). Clearly, candidemia is posing an increasingly serious problem in infectious diseases, and has been shown to be associated with 57% crude and 38% attributable mortality rates (12).

As neither the prevalence nor incidence of nosocomial fungal bloodstream infections in The Netherlands is known, the aim of this study was to identify trends in yeast bloodstream infections retrospectively in this country by evaluating computerized laboratory and census data from five of the eight Dutch university hospitals.

## Patients and Methods

Five university hospitals in The Netherlands participated in the study, including two hospitals in Amsterdam and one hos-

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**Table 1:** Overall episodes of yeast bloodstream infections in the study period.

| | 1987 | 1988 | 1989 | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | Mean ± SD |
|---|---|---|---|---|---|---|---|---|---|---|
| Yeasts (n=671) | | | | | | | | | | |
| Overall no | 57 | 48 | 70 | 64 | 73 | 70 | 111 | 78 | 100 | 74.6 ± 19.9 |
| No. per 10.000 PD | 0.40 | 0.34 | 0.51 | 0.46 | 0.54 | 0.50 | 0.82 | 0.58 | 0.76 | 0.55 ± 0.16 |
| *Candida* (n=625) | | | | | | | | | | |
| Overall no | 53 | 45 | 63 | 59 | 67 | 67 | 101 | 75 | 95 | 69.4 ± 18.4 |
| No. per 10.000 PD | 0.37 | 0.32 | 0.46 | 0.43 | 0.50 | 0.48 | 0.74 | 0.56 | 0.72 | 0.31 ± 0.15 |
| *Cryptococcus* (n=46) | | | | | | | | | | |
| Overall 09 | 4 | 3 | 7 | 5 | 6 | 3 | 10 | 3 | 5 | 5.1 ± 2.3 |
| No. per 10.000 PD | 0.03 | 0.02 | 0.05 | 0.03 | 0.04 | 0.02 | 0.07 | 0.02 | 0.04 | 0.035 ± 0.017 |

pital each in Rotterdam, Utrecht and Nijmegen. The overall bed capacity of these five hospitals, which serve as tertiary-care referral centres for roughly two-thirds of the population of The Netherlands, is approximately 5,500.

Episodes of fungemia were identified retrospectively from microbiology data systems using computer-generated lists of patients whose blood cultures yielded yeasts during the period from 1 January 1987 to 31 December 1995. All patients admitted to the study hospitals were eligible for enrollment. An episode of fungal bloodstream infection was defined as at least one positive blood culture yielding yeast during a single hospitalization period. The number of blood culture sets examined per year and the outcomes (negative, positive bacterial, positive fungal) were reported. All microbiological data were taken at face value, disregarding the different blood culture and identification systems used in the participating hospitals. Between 1991 and 1992 automated blood culture systems were implemented in all participating hospitals. None of the hospitals used the lysis centrifugation system. Census data to determine patient days were retrieved from the hospital information systems.

## Results

During the nine-year study period from 1987 to 1995, the five university hospitals delivered a total of 12,353,861 patient days of care, averaging 1,372,600 ± 32,300 (mean ± SD) patient days per year. The number of patient days decreased over the years (from 1,426,319 in 1987 to 1,322,338 in 1995). In contrast, the number of admissions (118,966 in 1987; 128,864 in 1995), and the number of blood cultures taken per year (34,450 in 1987; 49,203 in 1995), increased by 8.3% and 42.8%, respectively.

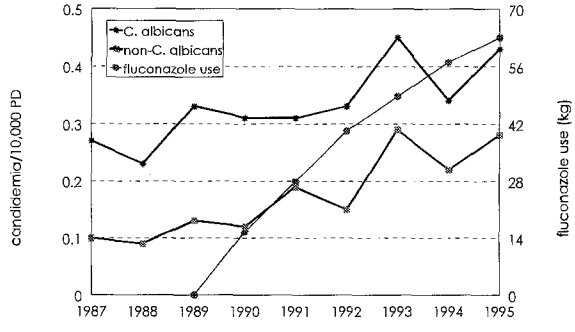


**Figure 1:** Episodes of *Candida albicans* and non-*Candida albicans* fungemia per 10,000 patient days (PD) in five Dutch university hospitals from 1987 to 1995 and the yearly use of fluconazole estimated from the nationwide sales figures for capsules (50, 150 and 200 mg) and vials (100 mg and 200 mg).

The proportion of positive blood cultures (with no regard for clinical significance) was 19% ± 2.9% (mean ± SD), remaining stable over the years. The proportion of positive blood cultures yielding yeasts ranged from 3.2% in 1988 to 5.6% in 1993.

Overall, 671 episodes of yeast bloodstream infections occurred during the study period (Table 1); 635 episodes (94.6 ± 2.9%) were due to *Candida* species, and 46 episodes (6.8%) were due to *Cryptococcus* species.

The rates of yeast bloodstream infections in The Netherlands during the study period are given as episodes per 10,000 patient days (Table 1). The lowest rate was seen in 1988 (0.34 episodes per 10,000 patient days), the highest rate in 1993 (0.82 episodes per 10,000 patient days). Figure 1 depicts the individual rates for *Candida albicans* and non-*Candida albicans*. During the study period, the rate of bacteremia increased from 15.2 episodes per 10,000 patient days to 23.5 episodes per 10,000 patient days in 1987 and 1995, respectively. Therefore, all rates showed the same increasing trend. Importantly, there was no significant difference between the rate of candidemia due to *Candida albicans* and non-*Candida albicans* species. During the study period, fluconazole was licensed for sale in The Netherlands. The annual use of fluconazole, estimated from the nationwide sale figures (data supplied by Pfizer, The Netherlands), increased by factor four from 15.5 kg in 1990 to 63.0 kg in 1995 (Figure 1).

The number of episodes of fungemia caused by the different *Candida* species and the proportion due to the individual non-*Candida albicans* species is

**Table 2:** Episodes of fungemia caused by individual *Candida* species and proportion of candidemia due to non-*Candida albicans* species in the study period.

| | 1987 | 1988 | 1989 | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 |
|---|---|---|---|---|---|---|---|---|---|
| *C. albicans* | 39 | 32 | 45 | 43 | 42 | 46 | 61 | 46 | 57 |
| Non-*C. albicans* | | | | | | | | | |
| *C. glabrata* | 3 | 3 | 5 | 3 | 5 | 2 | 14 | 10 | 16 |
| *C. tropicalis* | 2 | 1 | 2 | 1 | 3 | 1 | 3 | 4 | 4 |
| *C. krusei* | 2 | 1 | 0 | 0 | 1 | 0 | 0 | 2 | 2 |
| *C. parapsilosis* | 4 | 1 | 1 | 4 | 2 | 4 | 6 | 2 | 2 |
| *C. guillermondii* | 0 | 1 | 0 | 0 | 1 | 1 | 3 | 1 | 2 |
| Other species | 0 | 0 | 1 | 1 | 5 | 4 | 3 | 3 | 3 |
| Not determined* | 3 | 6 | 9 | 7 | 9 | 9 | 11 | 7 | 9 |
| Subtotal | 14 (26%) | 13 (29%) | 18 (29%) | 16 (27%) | 26 (38%) | 21 (31%) | 40 (40%) | 29 (39%) | 38 (40%) |
| Total | 53 | 45 | 63 | 59 | 68 | 67 | 101 | 75 | 95 |

* Mostly orginating from one study centre that only differentiated *C. albicans* and non-*C. albicans* species.

shown in Table 2. The increase of non-*Candida albicans* species was mainly due to *Candida glabrata*. Interestingly, the number of episodes of candidemia due to *Candida krusei* was very low throughout the study period (Figure 2). In the last year of the study period, 40% of all *Candida* bloodstream infections were due to non-*Candida albicans* species, *Candida glabrata* accounting for 42% or 55% of those episodes (depending on whether the figures for the non-determined species were included or not, see Table 2).

## Discussion

Major changes have occurred in hospital populations, health care technology and the use of antimicrobial drugs during the last two decades. Data from the National Nosocomial Infections Surveillance System and other hospitals in the USA show that these changes have had a profound impact on the epidemiology of fungal infections, including the increasing incidence of *Candida* bloodstream infections (1, 2, 13, 14). So far, only one European study has addressed the increasing problem of fungemia. Bruun et al. (15) showed an increase in the annual incidence of fungemia at a Danish university hospital from 19 episodes in 1989 to 57 episodes in 1994. Unfortunately, the authors gave no rates, thereby making it impossible to compare their findings with the literature and introducing the possibility of bias due to a likely increase in the number of blood cultures taken, as demonstrated in our study.

Pittet and Wenzel (16) reported a linear increase in the rates of nosocomial bloodstream infections at the University of Iowa Hospitals and Clinics (UIHC) between 1981 (67 episodes per 10,000 patient days) and 1992 (184 episodes per 10,000 patient days). Statistically significantly increased rates were demonstrated for the four predominant blood culture isolates coagulase-negative staphylococci, *Staphylococcus aureus*, enterococci and *Candida* species. Rates of candidemia increased 12-fold during the study period, reaching a peak of two episodes per 10,000 patient days in 1991 (16). The rates of bacteremia and candidemia found in Dutch university hospitals show the same increasing trend, but on a lower scale. In 1991, we found 0.5 episodes of candidemia per 10,000 patient days, a rate fourfold lower than the UIHC rate. Even three years after the end of the study in the USA, the rate of candidemia in Dutch university hospitals is still 2.8-fold lower (0.72 episodes per 10,000 patient days). In general, the rates of candidemia in The Netherlands are not only lower but the increase is less dramatic (2.3-fold compared to 12-fold at the UIHC). This difference between the USA and The Netherlands might be due to the very restricted antibiotic policy of Dutch physicians both within and outside the hospital, which is reflected in the low incidence of other multi-resistant pathogens, such as penicillin-resistant pneumococci, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococci (17–19).

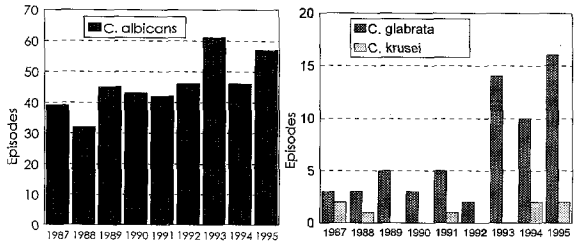


**Figure 2:** Occurrence of *Candida albicans*, *Candida glabrata* and *Candida krusei* among blood culture isolates in five Dutch university hospitals from 1987 to 1995.

Overall, 60% of all candidemic episodes in the study period were caused by *Candida albicans*, but the proportion of candidemic episodes due to non-*Candida albicans* species increased from 26% to 40%. This increase was due mainly to a rising number of episodes due to *Candida glabrata*, a *Candida* species with reduced susceptibility to fluconazole. During the study period, the rates of candidemia due to *Candida* species with reduced fluconazole susceptibility (*Candida glabrata* and *Candida krusei*) increased 4.7-fold (0.03 per 10,000 patient days in 1987 versus 0.14 per 10,000 patient days in 1995) compared to an 2.8-fold increase (0.06 per 10,000 patient days in 1987 versus 0.17 per 10,000 patient days in 1995) for the other non-*Candida albicans* species. However, other factors besides the increased use of fluconazole in The Netherlands may have contributed to this species shift and should be identified in future investigations.

Changes in blood culture techniques, most importantly the introduction of agitation (1991/92), may have influenced our general findings, but were not the only factors influencing the general trend since this would have resulted in a sudden increase with only minor changes in the period before and after the introduction.

To what degree demographic changes in patient population may have contributed to the observed trend is not clear. During the study period the number of admissions and thus the number of patients who could develop candidemia increased, but at the same time the average time of hospitalization decreased (from 12.1 days in 1987 to 10.3 days in 1995) thereby reducing the chance of the individual patient acquiring systemic candidiasis.

The introduction of new diagnostic and therapeutic techniques, and the increased and prolonged use of multiple antimicrobial agents in a growing proportion of severely ill patients (reflected in the growing number of blood cultures taken) may be other factors contributing to the increase of nosocomial *Candida* bloodstream infections in Dutch university hospitals.

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