Secular Trend of Hospital-Acquired Candidemia among Intensive Care Unit Patients in the United States during 1989–1999

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We describe the annual incidence of primary bloodstream infection (BSI) associated with *Candida albicans* and common non-*albicans* species of *Candida* among patients in intensive care units that participated in the National Nosocomial Infections Surveillance system from 1 January 1989 through 31 December 1999. During the study period, there was a significant decrease in the incidence of *C. albicans* BSI ($P < .001$) and a significant increase in the incidence of *Candida glabrata* BSI ($P = .05$).

Candida species commonly cause hospital-acquired bloodstream infections (BSIs) [1] among patients in the intensive care unit (ICU), and these infections are associated with high rates of morbidity and mortality [2, 3]. During the 1980s, an increased rate of candidemia in the United States was reported [4]. The introduction of triazoles, such as fluconazole, in the early 1990s provided a new option for treatment of systemic fungal infections. Fluconazole's efficacy was documented for both prevention [5, 6] and treatment [7] of *Candida* infection. One institution demonstrated that fluconazole use dramatically increased during the 1990s [8], which likely has occurred in many hospitals in the United States.

Certain *Candida* species (e.g., *Candida krusei* and *Candida glabrata*) have a tendency toward decreased susceptibility to fluconazole [9]. Therefore, the availability and increased use of fluconazole may be a factor in the emergence of *C. glabrata* infections reported from a hospital in the United States [8] and from other countries [10, 11]. To evaluate the trend in incidence of BSI due to different *Candida* species during the past decade, we analyzed data from 1989–1999 from the ICUs that report to the National Nosocomial Infections Surveillance (NNIS) system.

Methods. Hospitals in the NNIS system are not systematically selected, and participation is voluntary. Compared with other hospitals in the United States, those in the NNIS system tend to have more beds and an academic affiliation [12]. During 2000, >300 hospitals participated in ⩾1 of several components of the NNIS system. We analyzed data reported to the ICU component. A BSI was reported if it occurred during a patient's ICU stay or within 48 h after the patient was discharged from the ICU. Standardized NNIS definitions of BSI were used [13]. ICUs that submitted data for ⩾1 month from 1 January 1989 through 31 December 1999 (the study period) were included. We included only data for primary BSIs—that is, BSIs unrelated to infection at another site [13]. Susceptibility data were not reported to the NNIS system.

ICUs were categorized according to the predominant type of patient receiving cared in the ICU (i.e., ICUs in which ⩾80% of the patients were classified as a single type). Data were reported separately for burn, coronary, combined medical-surgical (with <80% of patients of a single type), medical, neurosurgical, pediatric, respiratory, surgical, and trauma ICUs. Patients in neonatal ICUs were excluded.

We calculated the pooled mean incidence of *Candida* BSI for the entire study period (i.e., the total number of BSIs divided by the total number of days in which a central venous catheter [CVC] was in place) for all *Candida* species and for each of the more common *Candida* species *(C. albicans, C. glabrata, C. parapsilosis, C. tropicalis,* and *C. krusei)*. We performed trend analyses on the device-associated BSI incidence, using the χ^2 test for trend. In addition, we describe the BSI incidence for different ICU types by pooling data among each of the types of ICUs, and we compare the BSI incidence between common ICU types (i.e., medical-surgical [either at nonteaching or teaching hospitals], surgical, medical, coronary, pediatric, and cardiothoracic ICUs). Differences in the distribution of ICU-specific incidence of *Candida* species BSI were tested using the Kolmogorov-Smirnov test. All analyses were performed using

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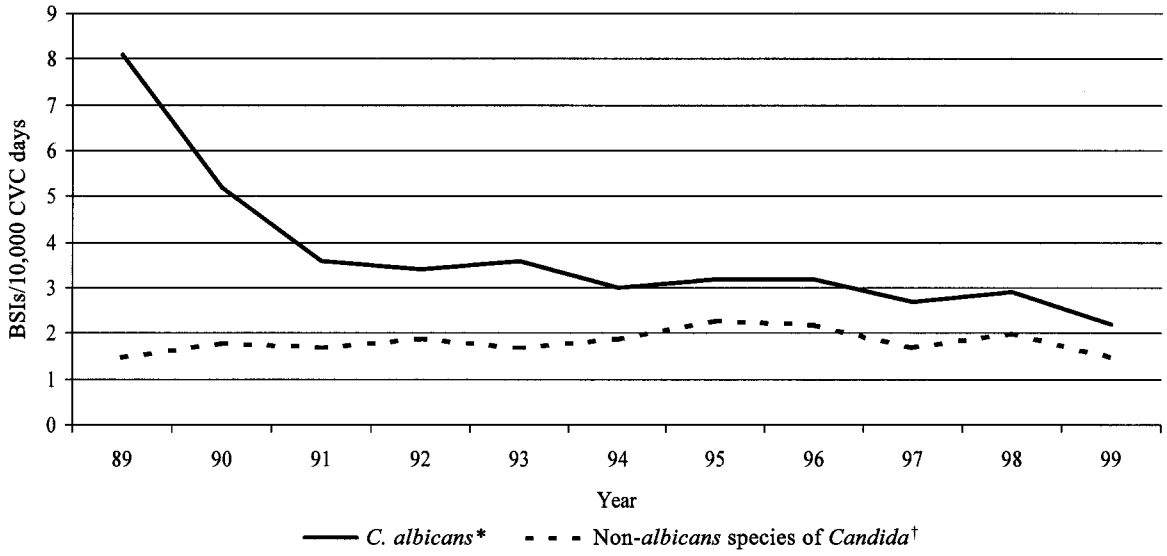

Figure 1. Incidence of hospital-acquired bloodstream infection (BSI) due to *Candida albicans* and non-*albicans* species of *Candida,* National Nosocomial Infections Surveillance system intensive care unit wards, 1989–1999. *$P < .001$ for the annual incidence of *C. albicans* BSI, determined using the χ^2 test for trend, 1989–1999. †$P = .53$ for the annual incidence of non-*albicans* species of *Candida* BSI, determined using the χ^2 test for trend, 1989–1999. CVC days, total no. of days in which a central venous catheter was in place.

Epi Info, version 6.03 (Centers for Disease Control and Prevention) [14], or SAS, version 6.12 (SAS Institute).

Results. From 1 January 1989 through 31 December 1999, 311 hospitals submitted data from 1116 ICUs. For all ICUs, there were 3,041,585 patients, accounting for 10,428,666 patient-days and 5,226,950 CVC days. Of the 1116 ICUs, 206 were medical-surgical ICUs at nonteaching hospitals, 178 were surgical ICUs, 164 were medical ICUs, 138 were medical-surgical ICUs at teaching hospitals, 132 were coronary ICUs, 95 were pediatric ICUs, 65 were cardiothoracic ICUs, 59 were neurosurgical ICUs, 29 were trauma ICUs, 22 were burn ICUs, 9 were respiratory ICUs, and 19 were other types of ICUs. The median number of months of data submitted by participating ICUs was 6 months per year. Of the 123 ICUs that reported data in 1989, 70 (57%) also reported data in 1999.

For all ICUs, 2759 BSIs associated with *Candida* species were reported. There were 2358 monomicrobial BSIs (85%) associated with *Candida* species. The incidence of monomicrobial BSI during the study period for all *Candida* species was 4.8 cases per 10,000 CVC days. *C. albicans* BSIs were the most common (59% of all *Candida* BSIs), followed by *C. glabrata* (12%), *C. parapsilosis* (11%), *C. tropicalis* (10%), and *C. krusei* (1.2%) BSIs. The distribution of *Candida* species among polymicrobial BSIs was similar to that of monomicrobial BSIs, and was as follows: *C. albicans* (57% of BSIs), *C. glabrata* (13%), *C. parapsilosis* (13%), *C. tropicalis* (12%), and *C. krusei* (0.7%). Uncommon *Candida* species (i.e., those responsible for <1% of all *Candida* BSIs) included *C. lusitaniae* ($n = 20$), *C. guilliermondii* ($n = 5$), *C. stellatoidea* ($n = 1$), and *C. pseudotropicalis* ($n = 1$).

The median age of patients who acquired a monomicrobial *Candida* BSI was 58 years (interquartile range, 40–70 years). Fifty-five percent were male, 93% had a CVC in place, and 56% received total parenteral nutrition at the time of infection.

Among the common ICU types, the incidence of BSI (expressed as number of BSIs per 10,000 CVC days) varied significantly ($P = .002$): in medical ICUs, 7.2; in pediatric ICUs, 6.4; in medical-surgical ICUs at teaching hospitals, 5.4; in surgical ICUs, 4.9; in medical-surgical ICUs at nonteaching hospitals, 4.5; in coronary ICUs, 3.0; and in cardiothoracic ICUs, 2.4.

During the study period, there was a significant decrease in the incidence of *C. albicans* BSI ($P < .001$), but the incidence of BSI due to non-*albicans* species of *Candida* remained stable ($P = .53$; figure 1). When the BSIs due to non-*albicans* species of *Candida* were analyzed by species, we noted a significant increase in the incidence of *C. glabrata* BSI ($P = .05$), which increased dramatically after 1993 (figure 2). Although *C. glabrata* was the most common non-*albicans* species of *Candida* associated with BSI during 1995–1999, there appeared to be a decreased incidence during this time period. When we evaluated trends in candidemia by ICU type, there was a significant decrease in the incidence of *C. albicans* BSI for surgical, medical-surgical at teaching and nonteaching hospitals, coronary, and pediatric ICU types.

Discussion. During 1989–1999, there was a significant de-

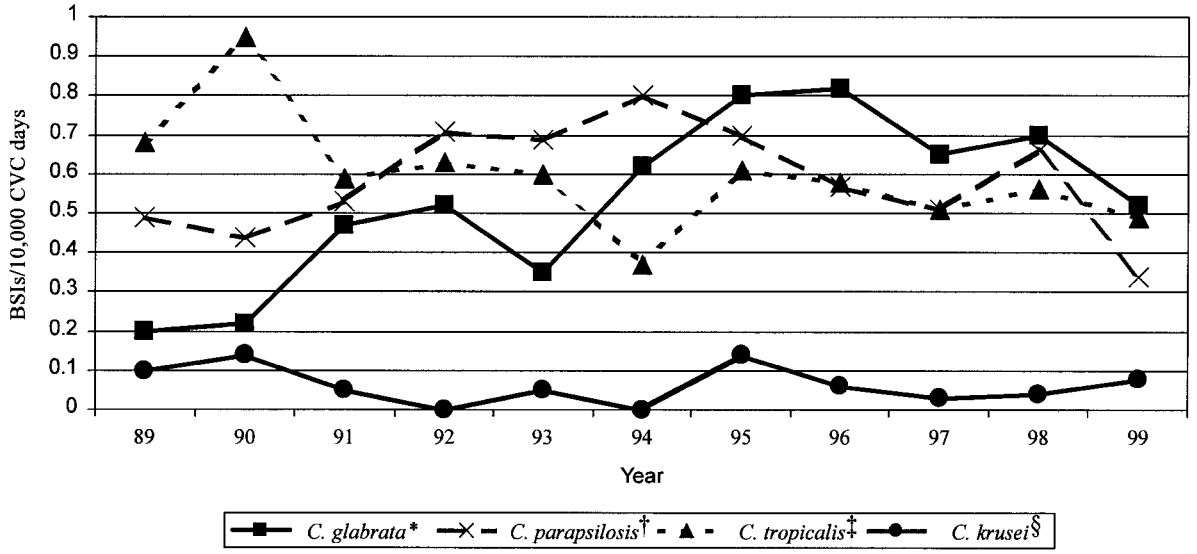

Figure 2. Incidence of hospital-acquired bloodstream infection (BSI) with non-*albicans* species of *Candida,* by species, National Nosocomial Infections Surveillance system intensive care unit wards, 1989–1999. *P = .05 for the annual incidence of *Candida glabrata* BSI. †P = not significant for the annual incidence of *Candida parapsilosis* BSI. ‡P = .16 for the annual incidence of *Candida tropicalis* BSI. §P = not significant for the annual incidence of *Candida krusei* BSI. CVC days, total no. of days in which a central venous catheter was in place.

crease in the incidence of hospital-acquired candidemia among ICU patients in NNIS system hospitals. This decrease was due to a decrease in the incidence of *C. albicans* BSI. We also documented a significant increase in the incidence of *C. glabrata* BSI. Although *C. glabrata* was the fourth most common *Candida* species associated with BSI in 1989, it was the second most common *Candida* species during 1995–1999.

Several factors may have contributed to the decreased incidence of *C. albicans* BSI. These include the fact that prophylactic use of fluconazole has likely increased, which has successfully decreased the incidence of *Candida* infection in specific clinical situations [5, 6, 15]. In addition, rates of BSIs associated with all bacterial and fungal pathogens have decreased [16], which suggests that the decreased incidence of *C. albicans* BSI may have occurred because of factors that affect the incidence of all types of BSIs (e.g., improved infection-control practices).

The increased incidence of *C. glabrata* BSI detected in our study is consistent with the findings of previous reports from other institutions [8, 11]. This increase likely has occurred in association with a national increase in fluconazole use, which received US Food and Drug Administration (FDA) approval in 1990. After it received FDA approval, a large increase in fluconazole use was reported from a single institution [8], and it has been shown that receipt of fluconazole can promote *C. glabrata* colonization in a select patient population [17]. Although a stable prevalence of fluconazole resistance among *C. glabrata* isolates from 1997–1999 has been reported [9], the increased incidence of *C. glabrata* BSI that we observed occurred during a different period (1990–1995) and in a separate patient population.

The increased incidence of *C. glabrata* BSI among ICU patients in the United States may be an important consideration during the application of guidelines for empiric treatment of patients with presumed fungal infection. For example, fluconazole has been recommended as a possible alternative to amphotericin B for the empiric treatment of neutropenic patients who continue to have fever despite receiving antibacterial therapy, although this is only recommended in institutions in which isolation of drug-resistant *Candida* species is uncommon [18]. The changing distribution of *Candida* BSI supports efforts to evaluate and define appropriate indications for fluconazole prophylaxis and empiric therapy.

The difference in *Candida* BSI rates between different types of ICUs may reflect the characteristics present among patients in each type of ICU. For example, known risk factors for candidemia include number of antimicrobial agents received, duration of antimicrobial therapy, receipt of total parenteral nutrition, neutropenia, hemodialysis, previous colonization, and extensive surgery or burns [19]. It also is possible that prophylactic use of fluconazole varied between ICU types.

Limitations of this study include the lack of detailed clinical information for individual patients. Some of our findings may be attributable to patient risk factors for which NNIS system hospitals do not routinely collect data. Also, we do not have data about ICU-specific fluconazole use, which would have

enabled us to perform analyses comparing fluconazole use between ICU types or correlating fluconazole use and rates of BSI due to non-*albicans* species of *Candida*. Because of these limitations, we can only speculate about the factors that contributed to the changing incidence of candidemia. Furthermore, because our analyses were restricted to the ICU patient population, we cannot draw any conclusions about *Candida* BSI rates for patients who receive health care outside of ICUs. It is possible that the incidence of candidemia among patients who received medical care outside of ICUs, (e.g., in non-ICU units, long-term care facilities, and the home) increased during 1989–1999, and a population-based surveillance study [20] might have identified different trends in the incidence of *Candida* BSI.

Among ICU patients, the incidence of *C. glabrata* BSI significantly increased and the incidence of *C. albicans* BSI significantly decreased during 1989–1999. Because therapeutic options and rates of antimicrobial resistance vary according to *Candida* species, detailed studies of risk factors are needed to guide decisions regarding empiric antifungal therapy, and ongoing surveillance is warranted to detect species-specific changes in the incidence of candidemia.

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