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Secular Trends in the Epidemiology of Nosocomial Fungal Infections in the United States, 1980–1990

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To identify pathogens causing nosocomial fungal infections and the secular trend in their incidence in US hospitals, data from the National Nosocomial Infections Surveillance System, 1980–1990, were analyzed. During that period, 30,477 fungal infections were reported. The rate rose from 2.0 to 3.8 infections/1000 discharges. The highest number of nosocomial fungal infections/1000 discharges was reported from the burn/trauma service (16.1). *Candida albicans* was the most frequently isolated fungal pathogen (59.7%), followed by other *Candida* species (18.6%). The rate increased at all four major anatomic sites of infection. Patients with bloodstream infections who had a central intravascular catheter were more likely to have a fungal pathogen isolated than were other patients with bloodstream infection (relative risk = 3.2; $P < .001$): 29% of fungemia patients and 17% of patients with bloodstream infection due to other pathogens died during hospitalization ($P < .001$). Fungi are emerging as important nosocomial pathogens and control efforts should target fungal infections, especially fungemia.

The past two decades have witnessed major changes in hospital populations and the technology of health care in the United States. Improvements in the prognosis of patients with cancer, immunodeficiencies, and connective tissue diseases have occurred. Organ transplantation and advances in immunomodulation have revolutionized the care of patients with end-stage renal, cardiac, and other diseases. Neonatal intensive care and advances in neonatal support, such as artificial surfactant, have greatly increased the survival of premature infants. The use of broad-spectrum antibiotics has greatly increased in the past 10 years, particularly among neutropenic patients. As a result of the increased and prolonged survival of these and other patient populations who are highly susceptible to infection, various institutions have reported an increase in their nosocomial fungal infection rate [1, 2]. These infections are often severe, rapidly progressive, difficult to diagnose, and refractory to therapy. To determine the temporal trends in fungal infections and to describe the epidemiology of nosocomial fungal infections in US hospitals, we analyzed data from the National Nosocomial Infections Surveillance (NNIS) System.

Methods

Study population. The data were collected from January 1980 through December 1990 by 115 hospitals participating in

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the NNIS System. These hospitals voluntarily conducted prospective surveillance on nosocomial infections and reported these data to the Centers for Disease Control (CDC) [3]. Before 1986, all hospitals participating in the NNIS System did hospitalwide surveillance. Beginning in 1986, three alternative standardized protocols or surveillance components were introduced: the adult and pediatric intensive care unit component, the high-risk nursery component, and the surgical patient component [3]. For hospitals conducting hospitalwide surveillance, denominator data reported included the number of discharges by month and hospital service.

The teaching affiliation and number of beds of NNIS hospitals were used to classify hospitals into four strata: small nonteaching (<200 beds), large nonteaching (≥200 beds), small teaching (<500 beds), and large teaching (≥500 beds) hospitals.

For each infection, up to four pathogens, an anatomic infection site, the service on which the patient was hospitalized at the time of the infection, selected demographic and potential risk factor information, and patient outcome were reported [3–5]. When infected patients died, surveillance personnel used information from the patient's medical records and other sources to subjectively assess the relationship of the infection to the death of the patient. They reported their conclusion that the infection caused the death, contributed to the death, or was unrelated or that the relationship was unknown.

Definitions. NNIS hospitals used uniform definitions of nosocomial infections, which attempt to include clinically significant hospital-acquired infections and exclude cultures containing only contaminants or colonizing organisms [6]. Nosocomial fungal infections included all infections meeting the CDC criteria from which *Candida albicans*, other *Candida* species, *Aspergillus* species, *Torulopsis* species, or other fungal pathogens were recovered.

Rate calculations. The number of nosocomial fungal infections/1000 discharges only in hospitals conducting hospitalwide surveillance was calculated to investigate trends in nosocomial fungal infection rates in NNIS hospitals. Rates of nosocomial fungal infection by hospital service, anatomic site, and year were calculated. To investigate the possibility of bias resulting from hospitals entering and leaving the NNIS sample, we then estimated changes in infection rates between consecutive years using only the data from hospitals that reported in both years and also confined analysis to hospitals that had participated in NNIS for at least 5 years.

To determine the pathogen distribution of nosocomial fungal infections, potential risk factors for nosocomial fungemia, and mortality due to nosocomial fungemia, we analyzed data from all surveillance components (i.e., hospitalwide, adult and pediatric intensive care unit, high-risk nursery, and surgical patient) [3].

To identify risk factors for fungemia, we compared the proportion of bloodstream infections that were fungal (fungal bloodstream infections/all bloodstream infection) by exposure status for each of several potential risk factors. The mortality rate among patients with fungal bloodstream infection was compared with the mortality rate among patients with bloodstream infection due to other pathogens. A bloodstream infection was considered to be related to a patient's death if surveillance personnel documented that the infection caused or contributed to the patient's death.

Statistical methods. Proportion ratios and 95% confidence intervals were calculated as estimates of relative risk [7]. Likelihood ratio test statistics and the corresponding P values were calculated to test for significant differences in infection or mortality rates [7].

Results

Temporal trends. During 1980–1990, NNIS hospitals reported 30,477 nosocomial fungal infections, of which 26,553 were reported by hospitals conducting hospitalwide surveillance. During this period, the nosocomial fungal infection rate at facilities conducting hospitalwide surveillance increased from 2.0 to 3.8 infections/1000 patients discharged (figure 1). This increase remained significant even after we adjusted for possible sample migration (1.3 to 2.9, $P < .001$) and confined analysis to the 73 hospitals that participated in NNIS for ≥5 years during the study period (2.0 to 3.9, $P < .001$). Increases were seen in all strata: Nosocomial fungal infection rates increased from 0.9 to 2.4, 1.2 to 2.5, 2.1 to 3.5, and 2.4 to 6.6 in small nonteaching, large nonteaching, small teaching, and large teaching hospitals, respectively.

Over the study period, the nosocomial fungal infection rate increased for urinary tract infection (from 9.0 to 20.5/10,000 discharges), for surgical wound infections (from 1.0 to 3.1), and for pneumonia (from 2.3 to 3.6). The nosocomial fungemia rate rose from 1.0 to 4.9.

The overall nosocomial fungal infection rate/1000 discharges in 1990 at NNIS hospitals conducting hospitalwide surveillance varied by major specialty service, with the lowest rates reported on the obstetric (0.2), newborn (1.0), gynecology (1.3), and pediatric (1.3) services and the highest rates on the medicine (5.2) and surgery (5.6) services; the nosocomial fungal infection rates rose during the study period on the major services (figure 1). The most marked increases occurred on the surgery (2.5 to 5.6/1000 discharges; 124% increase) and medicine services (3.0 to 5.2/1000 discharges; 73% increase).

From January 1986 through December 1990, subspecialty services in NNIS hospitals conducting hospitalwide surveillance with highest nosocomial fungal infection rates included the burn/trauma (16.1), cardiac surgery (11.2), oncology (8.6), high-risk nursery (7.6), and general surgery (7.3) services. During this period, increases in infection rate were reported in the cardiac surgery (8.9 to 14.8), burn/trauma (15.9 to 18.1), and high-risk nursery services (4.7 to 9.6); on the oncology service, the nosocomial fungal infection rate varied from 10.6 to 8.9.

The proportion of nosocomial infections reported by all hospitals due to fungal pathogens rose from 6.0% in 1980 to 10.4% in 1990 at all major sites of infection: surgical wound

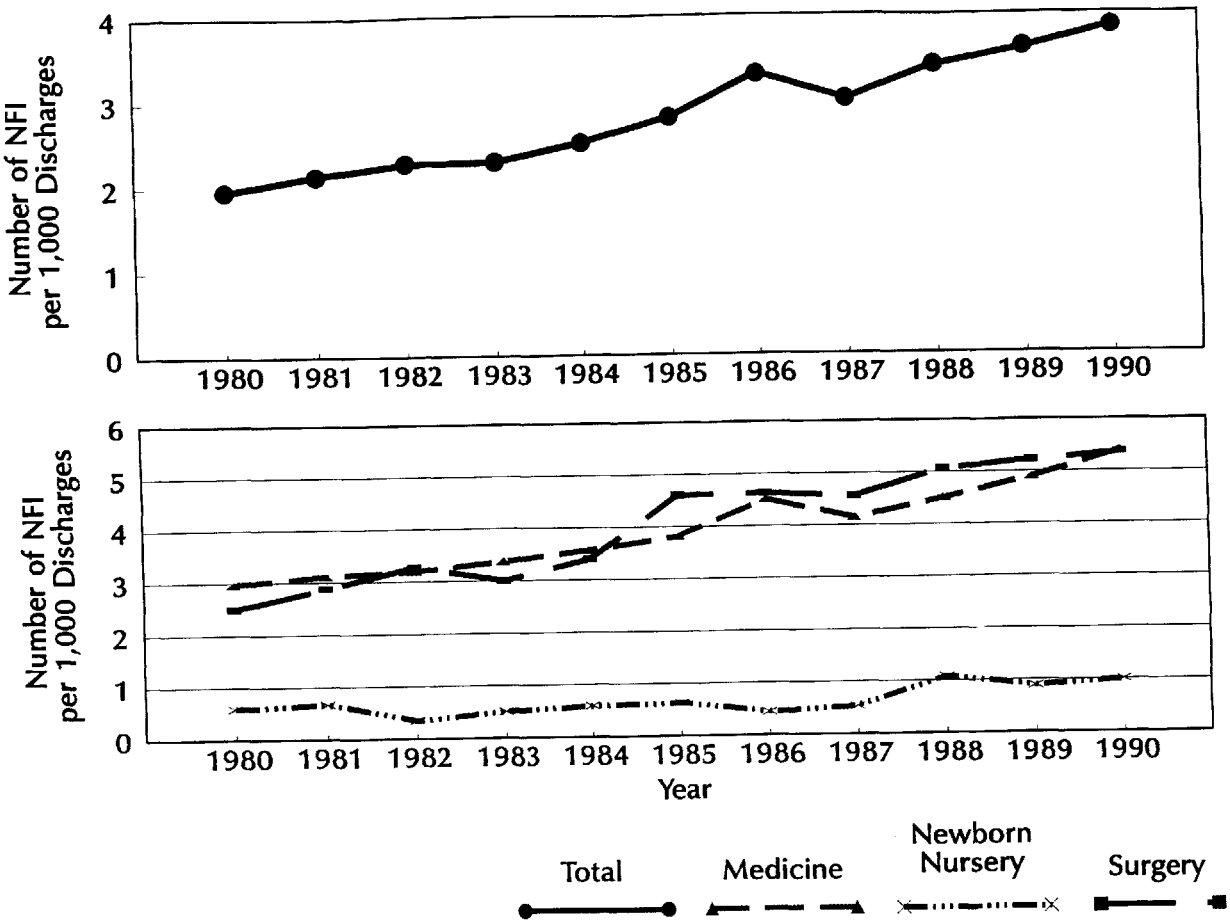

Figure 1. Secular trend in nosocomial fungal infection (NFI) rate at US hospitals, National Nosocomial Infections Surveillance System, total and by selected major services, 1980–1990.

infections, from 1.5% to 5.1%; lung infections, from 5.2% to 5.7%; urinary tract infections, from 6.7% to 18.7%; and bloodstream infections, from 5.4% to 9.9%.

Pathogens causing nosocomial fungal infections. *Candida* species infections accounted for 78.3% of nosocomial fungal infections reported to the NNIS System, followed by *Torulopsis* species (sometimes classified as *Cryptococcus glabrata*) (7.3%) and *Aspergillus* species (1.3%), which was the pathogen reported for many fungal pneumonias. *C. albicans* was the most frequently isolated fungal pathogen (59.7%), followed by other *Candida* species (18.6%). *C. albicans* accounted for 18,463 (76%) of 24,227 *Candida* infections. Throughout the study period, there was a relative increase in *C. albicans* infections (from 52% in 1980 to 63% in 1990) and a relative decrease in *Candida tropicalis* and other *Candida* infections (from 21% in 1980 to 16% in 1990).

Nosocomial fungemia. The proportion of bloodstream infections due to fungal pathogens varied by patient care characteristic. Patients with bloodstream infections who had a central intravascular catheter were more than three times as likely to have a fungal pathogen isolated (1840 [12.3%] of 14,963) as were patients with bloodstream infections who did not have a central intravascular catheter (276 [3.8%] of 7240; $P < .001$) (table 1). Likewise, patients with bloodstream infections receiving total parenteral nutrition or in intensive care units were more likely to have fungemia (15.6% and 11.0%, respectively) than were those not receiving total parenteral nutrition (6.4%) or not in intensive care units (8.1%). When parenteral nutrition was controlled for, central intravascular catheterization was still significantly associated with fungemia. Among patients with central intravascular catheters receiving total parenteral nutrition who developed bloodstream infections, those in intensive care units were still somewhat more likely to have fungemia (relative risk, 1.2; 95% confidence interval, 1.1–1.4).

Patients with fungemia were more likely to die during hospitalization (954 [29%] of 3256) than were patients with bloodstream infection due to nonfungal pathogens (5594 [17%] of 33,882; relative risk, 1.8; 95% confidence interval, 1.7–1.9; $P < .001$). Patients with fungemia who died were

Table 1. Comparison of selected potential risk factors for nosocomial fungal bloodstream infections, National Nosocomial Infections Surveillance System, January 1985–December 1990.

Potential risk factor	Fungal bloodstream infections (n = 2355)	All bloodstream infections (n = 24,511)	Proportion that were fungal*	Relative risk†	95% CI‡
Central catheterization					
Yes	1840	14,963	12.3	3.2	2.9–3.7
No	276	7240	3.8		
Total parenteral nutrition					
Yes	1319	8431	15.6	2.5	2.3–2.7
No	983	15,429	6.4		
Intensive care unit					
Yes	1415	12,906	11.0	1.4	1.3–1.5
No	940	11,605	8.1		

NOTE. Analysis was confined to patients with risk factor information. Information regarding intensive care unit hospitalization and use of parenteral nutrition and central vascular catheterization was not collected before 1985.

* No. of fungal bloodstream infections/all bloodstream infections × 100.

† Proportion that were fungal with risk factor/proportion that were fungal without risk factor.

‡ 95% confidence interval ($P < .001$).

slightly more likely to have infection control personnel report that the death was related to the infection than were those who died with nonfungal bloodstream infections (658 [88%] of 744 vs. 3410 [78%] of 4435; relative risk, 1.13; 95% confidence interval, 1.10–1.16).

Discussion

These data suggest that fungi have increased in importance as nosocomial pathogens in US hospitals, as has been observed in prior reports [1, 2]. The temporal increase appears to have occurred in all NNIS hospitals regardless of size or teaching affiliation and on all major services. Large increases were noted in the high-risk nursery, burn/trauma, and cardiac surgery subspecialty services. Interestingly, the oncology service did not show an increase from 1986 to 1990.

The most dramatic increase occurred in the fungemia rate. This may reflect, in part, the overall rise in bloodstream infections due to all pathogens observed in US hospitals in the 1980s [8]. Our data suggest an association between fungemia and total parenteral nutrition. Previous outbreaks of *Candida parapsilosis* fungemia have been traced to contaminated vacuum pumps used to prepare parenteral nutrition solutions, central intravascular pressure monitoring, and use of parenteral nutrition in immunocompromised hosts [9, 10]. In the endemic setting as well, fungemia, especially with *C. albicans*, has been associated with parenteral nutrition [11]. Multiple studies of growth properties of fungi in parenteral nutrition solutions have established that these solutions preferentially support the growth of several *Candida* species [12]. Skin colonizers, particularly *C. albicans*, can also gain access to the bloodstream directly during prolonged central catheterization used for parenteral nutrition, the mechanism most likely to explain the pathogenesis of catheter-related endemic bloodstream infection.

Use of central intravascular catheterization, which we found was strongly associated with fungal bloodstream infection, has been identified previously as a risk factor for *Candida* fungemia [13]. This may be related to the higher rate of catheter colonization with skin flora, including *C. albicans*, observed in patients with central catheters. Use of systemic antimicrobials and polyantimicrobial ointments in patients with central catheters may contribute to prevalence of *Candida* species in catheter-related infections [13].

The pathogens associated with nosocomial fungal infections differed markedly from those causing community-acquired infections. While *Candida* infections accounted for 78% of nosocomial fungal infections, in one report community-acquired fungal infections were caused by *Histoplasma capsulatum* (28%), *Coccidioides immitis* (23%), and *Aspergillus* species (17%) [14]. The risk factors described above, including central catheter and total parenteral nutrition use as well as hospitalization in an intensive care unit, may explain much of the observed difference.

Although mortality associated with nosocomial fungemia may be related to fatal underlying disease processes that predispose to fungal infection, in our study most deaths in patients with fungemia were believed to be related to the infection. Other studies have indicated that *Candida* bloodstream infections have been associated with higher morbidity and mortality than seen in bloodstream infections with nonfun-

gal organisms [15]. This increased mortality may result from delay in diagnosis, difficulty in treating fungemia, and the association of fungemia with invasive but essential components of patients' care, such as central venous catheterization.

Several characteristics of the NNIS System may limit how representative these data are of all US hospitals. First, the hospitals participating in NNIS have changed through the study period; some of the hospitals participating now were not participating in 1980, and vice versa. However, controlling for year-to-year sample migration increased rather than reduced the marked increase in the nosocomial fungal infection rate. Compared with all US hospitals, NNIS hospitals overrepresent teaching hospitals and underrepresent small, nonteaching hospitals [3]. However, even when hospitals were stratified by size and teaching affiliation, increases in the rate of nosocomial fungal infection were observed in all strata. Because the rates in the trend analysis are aggregate rates rather than a median of individual hospitals' rates, comparison of these rates with a specific hospital's or ward's nosocomial fungal infection rates should be made cautiously if at all. While the introduction of specialized surveillance components should not have affected hospitalwide surveillance, which has continued according to the same protocol during the study period, it may have affected the number of infections that were reported from intensive care units. However, these infections were not used for trend analyses, which were confined to the hospitalwide component. Moreover, the trend towards increase was clearly established years before 1986, when the specialized components were added.

Though standardized definitions should provide uniformity in reporting of true infections, no validation study to independently confirm infection status and pathogens has been conducted. This may be of concern for certain sites such as lungs, where it is difficult to differentiate colonization from true infection. It is of much less concern for sterile sites, such as the bloodstream.

Trends toward increased use of central catheterization and other interventions that appear to increase the risk of fungemia in this analysis have been identified. These trends, as well as increased survival and use of broad-spectrum antimicrobial therapy in hospitalized patients, may help explain the emergence of fungi in the 1980s as nosocomial pathogens.

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