MAJOR ARTICLE

Risk Factors for Candidal Bloodstream Infections in Surgical Intensive Care Unit Patients: The NEMIS Prospective Multicenter Study

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See the editorial commentary by Sobel and Rex on pages 187–90.

To assess risk factors for development of candidal blood stream infections (CBSIs), a prospective cohort study was performed at 6 sites that involved all patients admitted to the surgical intensive care unit (SICU) for >48 h over a 2-year period. Among 4276 such patients, 42 CBSIs occurred (9.82 CBSIs per 1000 admissions). The overall incidence was 0.98 CBSIs per 1000 patient days and 1.42 per 1000 SICU days with a central venous catheter in place. In multivariate analysis, factors independently associated with increased risk of CBSI included prior surgery (relative risk [RR], 7.3), acute renal failure (RR, 4.2), receipt of parenteral nutrition (RR, 3.6), and, for patients who had undergone surgery, presence of a triple lumen catheter (RR, 5.4). Receipt of an antifungal agent was associated with decreased risk (RR, 0.3). Prospective clinical studies are needed to identify which antifungal agents are most protective and which high-risk patients will benefit from antifungal prophylaxis.

Over the past 2 decades, *Candida* species have become the fourth most common cause of bloodstream infections (BSIs) among patients in intensive care units (ICUs) [1–5]. Previous studies have suggested that possible risk factors for candidal BSI (CBSI) may include receipt of antibiotic agents, chemotherapy, or steroids; the presence of intravascular catheters; receipt of parenteral nutrition; surgery; hospitalization in an ICU; malignancy; neutropenia; and prior fungal colonization [2, 3, 6–14]. These data are limited by the fact that the large majority of studies have been retrospective, with data gathered from a single institution over a long period of time (e.g., a decade or more) [14].

Among patients cared for in ICUs, those in surgical ICUs (SICUs) are thought to be at the greatest risk for developing a CBSI [15, 16]. Given reports of the 40%–60% mortality rate associated with CBSIs, the use of antifungal prophylaxis for surgical patients has emerged as a common practice. However, there are no

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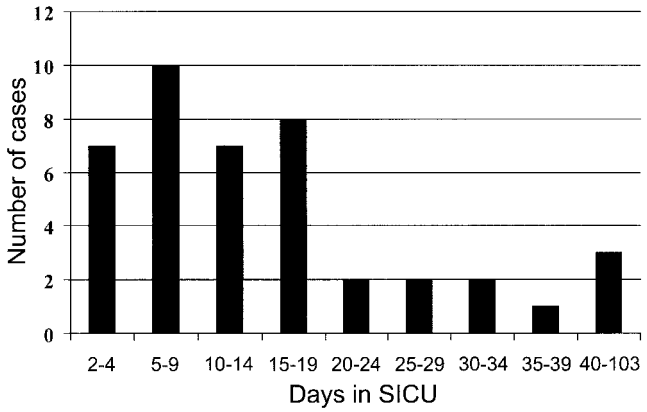

Figure 1. Time (in days) of onset of candidal bloodstream infection (BSI) after admission to a surgical intensive care unit (SICU). Forty-two candidal BSIs occurred during the study period.

data to indicate whether such use is beneficial in the ICU setting [17, 18].

The National Epidemiology of Mycosis Survey (or NEMIS) was a prospective, multicenter study conducted at 6 geographically dispersed academic medical centers to examine rates of and risk factors for the development of CBSIs among patients in surgical and neonatal ICUs. A recent report from the NEMIS study group has described the methods employed in the surveillance and the great variation in the rate of CBSIs among patients in surgical and neonatal ICUs at various institutions [19]. Herein we describe the risk factors for the development of CBSIs among patients being cared for in SICUs, and we report results of molecular typing and susceptibility tests performed on *Candida* species isolates recovered from blood cultures.

PATIENTS AND METHODS

Study design. The NEMIS was a prospective multicenter cohort study conducted in SICUs at 6 sites in the United States [19]: Atlanta (Grady Memorial Hospital/Emory University School of Medicine); Iowa City, Iowa (University of Iowa); Los Angeles (Harbor–UCLA Medical Center); New York City (Columbia-Presbyterian Medical Center); Portland (Oregon Health Sciences University); and San Antonio (University of Texas–San Antonio Health Sciences Center and the Veterans Affairs Medical Center). The study period was from October 1993 to November 1995, but the study was initiated and data were collected slightly later at some centers than at others. All centers enrolled patients for a minimum of 18 months.

Study population and case definition. All patients admitted to an SICU at these centers for >48 h were enrolled in the study. Case patients were defined as those individuals who had a *Candida* species recovered from culture of a blood specimen collected >48 h after admission to the SICU. For case patients, risk factor analysis included data collected up to the time of the development of the CBSI, whereas for non–case patients in the cohort, risk factor analyses included data collected for the entire duration of the stay in the SICU.

Data abstraction. Clinical and epidemiological data on all patients enrolled in the study were collected daily by dedicated study nurses, as previously described [19]. In the first year of the study, all azole drug use was recorded as a single variable, whereas in the second year information was recorded about the specific azole drugs administered (e.g., fluconazole, itraconazole, ketoconazole, miconazole, or clotrimazole). Severity-of-illness measures, including American Society of Anesthesia (ASA) scores [20], Acute Physiology and Chronic Health Evaluation (APACHE) II scores [21], and McCabe-Jackson scores [22], were calculated for all patients at the time of admission to the SICU.

Microbiological testing. Rectal swabs and urine specimens for fungal surveillance culture were collected from each patient at the time of admission to the SICU and each week thereafter if the patient remained hospitalized in the SICU. Fungal surveillance cultures were incubated according to standard laboratory methods and isolates were identified with use of the commercial identification system API20C and VITEK Yeast Identification (bioMérieux VITEK) [23]. Antifungal susceptibility of *Candida* species isolates was determined by testing them against amphotericin B, flucytosine, fluconazole, and itraconazole with use of a standard broth-microdilution method, as described elsewhere [24]. Molecular typing of *Candida* species isolates was performed by means of pulsed-field gel electrophoresis with use of the restriction enzyme *BssH*II or *Sfi*I [23]; *Candida albicans* isolates were typed with use of the species-specific probe Ca3 [25]. Thirty-five of 42 *Candida* species isolates recovered from blood were available for typing. Banding patterns were analyzed for relatedness with use of a computer-assisted system (Dendron software, version 2.0; Solltech).

Statistical analysis. Infection rates (the number of CBSIs per 1000 patient-days) were compared between groups of persons in different categories of the variable examined; the rate ratio was used as a measure of relative risk [26]. Univariate and multivariate analyses were performed with SAS software (SAS). A P value of $\leq .05$ was considered significant.

A stepwise approach was used to determine which of the studied factors or variables were most strongly associated with CBSI. Variables with significant colinearity were dropped from the analysis. The remaining variables were evaluated for associations with the development of CBSI with use of proportional hazards and logistic regression [27, 28]. Because both methods yielded similar results, only the results from the analysis per-

Table 1. Characteristics of 4276 surgical intensive care unit patients and their risk for candidal bloodstream infection.

Patient characteristic	No. (%) of patients		Infection rate[a]	RR (95% CI)	*P*
	All	Case patients			
Age, years					
4–24	331 (8)	3 (7)	0.99	—	
25–44	1118 (26)	10 (24)	0.84	0.8 (0.2–3.0)	.77
45–64	1558 (36)	19 (45)	1.27	1.5 (0.7–3.3)	.27
⩾65	1269 (30)	10 (24)	0.81	0.8 (0.2–2.9)	.74
Sex					
Male	2644 (62)	28 (67)	1.02	—	
Female	1632 (38)	14 (33)	0.94	0.9 (0.5–1.8)	.47
Location hospitalized[b]					
Oregon	687 (16)	2 (5)	0.28	—	
UCLA	749 (17)	3 (7)	0.50	1.9 (0.3–11.5)	.47
Texas	460 (12)	6 (14)	1.00	3.2 (0.6–15.9)	.16
Iowa	1006 (23)	11 (26)	1.13	4.0 (0.9–17.9)	.07
Grady	1029 (24)	16 (38)	1.43	4.8 (1.1–20.9)	.04
Columbia	345 (8)	4 (10)	1.75	7.5 (1.4–41.3)	.02
McCabe and Jackson disease score					
Nonfatal	1848 (43)	17 (40)	0.96	—	
Ultimately fatal	1468 (34)	13 (31)	0.96	1.0 (0.5–2.1)	1.00
Rapidly fatal	948 (22)	12 (29)	1.10	1.1 (0.5–2.3)	.83
APACHE II score					
0–11	946 (22)	5 (12)	0.82	—	
12–17	991 (23)	6 (14)	0.69	0.7 (0.2–2.4)	.59
18–24	1157 (27)	10 (24)	0.83	0.8 (0.3–2.3)	.66
25–47	1159 (27)	21 (50)	1.37	1.2 (0.5–3.3)	.70
ASA score (surgery patients only)					
1–2	600 (14)	2 (5)	0.43	—	
3	1434 (35)	14 (37)	1.01	1.1 (0.4–2.9)	.81
4–5	947 (23)	21 (55)	1.65	1.6 (0.7–4.1)	.28

NOTE. APACHE II, Acute Physiology and Chronic Health Evaluation II; ASA, American Society of Anesthesia.

[a] Cases of candidal bloodstream infection per 1000 days in the surgical intensive care unit.

[b] Hospital designations are as follows: Oregon, University of Oregon Health Sciences Center, Portland, OR; UCLA, Harbor-UCLA Medical Center, Los Angeles; Texas, University of Texas–San Antonio Health Sciences Center and the Veterans Affairs Medical Center, San Antonio; Iowa, University of Iowa, Iowa City; Grady, Grady Memorial Hospital/Emory University School of Medicine, Atlanta; and Columbia, Columbia-Presbyterian Medical Center, New York.

formed with proportional hazards regression are presented. In order to evaluate whether risk factors for the development of CBSI were different for SICU patients who did and did not have surgery, 2 regression models were used (one that included all patients in the study and another that included only those who had undergone surgery). During regression modeling, all variables that did not significantly contribute to the model were removed from consideration with use of a backward stepwise method. Regardless of statistical significance, the hospital variable was left in both models to account for potential unmeasured differences between different institutions in the risk of developing CBSI.

RESULTS

During the study period, 42 CBSIs developed among the 4276 admitted patients enrolled at the 6 different academic medical centers (9.82 CBSIs per 1000 admissions). *Candida* species accounted for 9.2% of the total number of BSIs ($n = 458$). The overall rate of CBSIs was 0.98 per 1000 SICU patient-days, or

Table 2. Infection rates and risk of candidal bloodstream infection for 4276 surgical intensive care unit patients, by type of procedure.

Procedure undergone	No. (%) of patients		Infection rate[a]	RR (95% CI)	*P*
	All	Case patients			
Intubation					
No	1021 (24)	2 (5)	0.30	—	
Yes	3255 (76)	40 (95)	1.12	2.7 (0.6–11.2)	.18
Central venous catheter					
No	1330 (31)	1 (2)	0.11	—	
Yes	2946 (69)	41 (98)	1.23	8.1 (1.1–59.6)	.04
Triple-lumen catheter					
No	2050 (48)	3 (7)	0.21	—	
Yes	2226 (52)	39 (93)	1.40	5.1 (1.5–16.8)	.01
Foley catheter					
No	675 (16)	4 (10)	0.71	—	
Yes	3601 (84)	38 (90)	1.04	1.3 (0.5–3.8)	.59
Hemodialysis					
No	4106 (96)	34 (81)	0.86	—	
Yes	170 (4)	8 (19)	2.79	2.6 (1.2–5.6)	.02
Surgery					
Any					
No	1075 (25)	1 (2)	0.11	—	
Yes	3201 (75)	41 (98)	1.22	8.7 (1.2–63.5)	.03
Abdominal					
No	2225 (52)	19 (45)	0.89	—	
Yes	976 (23)	22 (52)	1.78	1.8 (0.9–3.4)	.06
No surgery	1075 (25)	1 (2)	0.11	—	
Thoracic					
No	2949 (69)	39 (93)	1.26	—	
Yes	252 (6)	2 (5)	0.75	0.6 (0.1–2.6)	.51
No surgery	1075 (25)	1 (2)	0.11	—	
Cardiac/vascular					
No	2610 (61)	37 (88)	1.30	—	
Yes	591 (14)	4 (10)	0.79	0.7 (0.2–1.9)	.45
No surgery	1075 (25)	1 (2)	0.11	—	
Orthopedic					
No	2863 (67)	39 (93)	1.30	—	
Yes	338 (8)	2 (5)	0.55	0.4 (0.1–1.8)	.25
No surgery	1075 (25)	1 (2)	0.11	—	
Neurosurgery					
No	2624 (61)	39 (93)	1.47	—	
Yes	577 (14)	2 (5)	0.28	0.2 (0.1–0.7)	.02
No surgery	1075 (25)	1 (2)	0.11	—	
Ear/nose/throat					
No	2795 (65)	34 (81)	1.32	—	
Yes	406 (10)	7 (17)	0.89	0.5 (0.2–1.2)	.11
No surgery	1075 (25)	1 (2)	0.11	—	
Gynecological					
No	3180 (74)	41 (98)	1.23	—	
Yes	21 (1)	0 (0)	0	Undefined	
No surgery	1075 (25)	1 (2)	0.11	—	
Transplantation					
No	3103 (73)	41 (98)	1.25	—	
Yes	98 (2)	0 (0)	0	Undefined	
No surgery	1075 (25)	1 (2)	0.11	—	
Other					
No	2844 (67)	38 (91)	1.30	—	
Yes	357 (8)	3 (7)	0.68	0.5 (0.2–1.7)	.28
No surgery	1075 (25)	1 (2)	0.11	—	

[a] Cases of candidal bloodstream infection per 1000 days in the surgical intensive care unit.

Table 3. Treatments and medications associated with increased risk of candidal bloodstream infection in 4276 surgical intensive care unit patients.

Treatment or drug received	No. (%) of patients		Infection rate[a]	RR (95% CI)	*P*
	All	Case patients			
Parenteral nutrition					
No	3376 (79)	12 (29)	0.43	—	
Yes	900 (21)	30 (71)	2.04	3.8 (1.9–7.6)	<.001
Intralipid agents					
No	3514 (82)	20 (48)	0.67	—	
Yes	762 (18)	22 (52)	1.80	2.2 (1.2–4.0)	.02
Vancomycin					
No	2954 (69)	15 (36)	0.67	—	
Yes	1322 (31)	27 (64)	1.35	1.5 (0.8–2.8)	.26
Anti-anaerobic agents					
No	2600 (61)	10 (24)	0.50	—	
Yes	1676 (39)	32 (76)	1.44	2.2 (1.1–4.6)	.03

[a] Cases of candidal bloodstream infection per 1000 days in the surgical intensive care unit.

1.42 per 1000 SICU central line days (i.e., days in the SICU with a central venous catheter in place). Over half of the *Candida* isolates recovered from blood were non-*albicans* species: 20 (48%) were *C. albicans,* 10 (24%) were *Candida glabrata,* 8 (19%) were *Candida tropicalis,* 3 (7%) were *Candida parapsilosis,* and 1 (2%) was *Candida lusitaniae.*

Most CBSI cases (76%) occurred within the first 3 weeks of admission to an SICU (figure 1). The mortality rate was significantly higher among patients who developed CBSI than among other patients; 17 (41%) of 42 patients with CBSI died, versus 351 (8%) of 4234 patients who did not develop CBSI (OR, 7.52; 95% CI, 3.9–14.6; $P < .001$).

Risk factors. The mean age ($\pm$SD) of all patients enrolled in the study was 53.5 $\pm$ 18.2 years, which did not differ significantly from the mean age of those who developed CBSI (52.1 $\pm$ 17.5 years). Rates of CBSI varied between institutions, from a low of 0.28 per 1000 patient-days at the Oregon Health Sciences Center to a high of 1.75 per 1000 patient-days at Columbia-Presbyterian Hospital [19]. In univariate analysis, the CBSI rates at Grady Memorial Hospital and Columbia-Presbyterian Hospital were significantly higher than that at Oregon (table 1), but in multivariate analyses, residence at a particular institution was not associated with an increased risk of CBSI infection (see the section on Multivariate Analysis, below). A higher severity-of-illness value, as indicated by the McCabe-Jackson, APACHE II, or ASA score at the time of admission to the SICU, was not associated with increased risk of developing a CBSI in univariate analysis (table 1).

Of 42 patients who developed CBSIs, 41 had a central venous catheter (CVC) in place during their SICU stay prior to the development of infection (table 2). Among these 41 patients, the rate of CBSIs was 1.23 per 1000 patient-days, versus 0.11 per 1000 patient-days among patients who did not have a CVC in place (RR, 8.1; 95% CI, 1.1–59.6; $P = .04$). Seventy-five percent of SICU patients underwent surgery; this group had a significantly higher rate of CBSI than did the group who did not require surgery (table 2). There was a trend toward increased risk of infection among those who had an abdominal procedure performed (RR, 1.8; 95% CI, 0.9–3.4; $P = .06$); those

Table 4. Antifungal medications administered to 4276 surgical intensive care unit patients and their risk for candidal bloodstream infection.

Antifungal agent administered	No. (%) of patients		Infection rate[a]	RR (95% CI)	*P*
	All	Case patients			
Any					
No	3222 (75)	26 (62)	1.06	—	
Yes	1054 (25)	16 (38)	0.90	0.6 (0.3–1.1)	.09
Amphotericin B					
No	4107 (96)	40 (95)	1.05	—	
Yes	169 (4)	2 (5)	0.50	0.3 (0.1–1.4)	.14
Azole					
No	3774 (88)	31 (74)	0.98	—	
Yes	502 (12)	11 (26)	1.03	1.0 (0.5–2.1)	.86
Nystatin					
No	3791 (89)	35 (83)	1.01	—	
Yes	485 (11)	7 (17)	0.93	0.7 (0.3–1.7)	.48

[a] Cases of candidal bloodstream infection per 1000 days in the surgical intensive care unit.

Table 5. Clinical diagnoses assigned to 4276 surgical intensive care unit patients and their risk for candidal bloodstream infection (BSI).

Diagnosis	No. (%) of patients		Infection rate[a]	RR (95% CI)	*P*
	All	Case patients			
Acute renal failure					
No	3848 (90)	19 (45)	0.54	—	
Yes	428 (10)	23 (55)	3.09	4.7 (2.5–8.8)	<.001
Shock					
No	3458 (81)	17 (40)	0.57	—	
Yes	818 (19)	25 (60)	2.00	2.9 (1.5–5.4)	.001
ARDS					
No	3728 (87)	25 (60)	0.80	—	
Yes	548 (13)	17 (40)	1.55	1.5 (0.8–2.8)	.23
DIC					
No	3675 (86)	23 (55)	0.67	—	
Yes	601 (14)	19 (45)	2.31	3.0 (1.6–5.5)	<.001
Bacterial BSI					
No	3860 (90)	27 (64)	0.85	—	
Yes	416 (10)	15 (36)	1.44	1.2 (0.6–2.3)	.58

NOTE. ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation.

[a] Cases of candidal BSI per 1000 days in the surgical intensive care unit.

who had a neurosurgical procedure performed were at significantly lower risk (RR, 0.2; 95% CI, 0.1–0.7; $P = .02$), and no increased or decreased risk was seen among patients who underwent orthopedic, cardiovascular, ear/nose/throat, gynecologic, or transplantation surgery (table 2).

Medications associated with an increased risk of developing a CBSI in univariate analysis included receipt of parenteral nutrition, intralipid agents, vancomycin, or an antibiotic agent with activity against anaerobic organisms (including combinations of imipenem, metronidazole, clindamycin, and the extended-spectrum penicillins/β-lactamase-inhibitor drugs, such as ticarcillin/clavulanate, piperacillin/tazobactam, and ampicillin/sulbactam; table 3). Treatment with antifungal agents (amphotericin B, azoles, nystatin, or any antifungal drug) were not significantly associated with risk for developing CBSI in univariate analysis (table 4); however, in univariate analysis there was a trend toward an association between receipt of antifungal agents and a decreased risk of developing CBSI (RR, 0.6; 95% CI, 0.3–1.1; $P = .09$; table 4).

No increased risk of developing infection was associated with the individual use of the following antibiotic agents: aminoglycosides, penicillins (including extended-spectrum penicillins and β-lactam/β-lactamase inhibitor drugs), first-, second-, or third-generation cephalosporins, imipenem, fluoroquinolones, clindamycin, metronidazole, and erythromycin (data not shown). There were no CBSIs among the 784 SICU patients who did not receive an antibiotic agent. For the 3512 patients who did receive $\geq$1 antibiotic agents, there was no significant difference in rates of CBSIs with stratification by the number of days antibiotic agents were received (data not shown). Receipt of antacids, H_2 blockers, corticosteroids, or sucralfate also was not associated with risk of developing CBSI (data not shown).

Among patients who developed acute renal failure, shock, or disseminated intravascular coagulation, the rate of CBSI was significantly higher than it was among patients who did not develop these conditions (table 5). Among patients who had acute respiratory distress syndrome or developed a bacterial BSI, the rate of subsequent CBSI was higher than among patients who did not develop these conditions, but the differences were not statistically significant (table 5).

Risk after colonization. As part of the study protocol, rectal swabs and urine specimens for *Candida* surveillance cultures were collected on admission to the SICU and then weekly for patients who remained hospitalized in the SICU. Thirty percent of patients ($n = 1280$) had *Candida* species recovered in rectal surveillance cultures, and 15% of patients ($n = 627$) had a positive urine culture for *Candida* species (table 6). The positive predictive value for developing CBSI after a rectal culture was positive for *Candida* was only 2.0% (26/1280), and for a positive urine culture it was 2.7% (17/627). Among patients who had *Candida* species recovered from urine, the rate

Table 6. Fungal colonization among the 4276 surgical intensive care unit patients and their risk of candidal bloodstream infection.

Isolate and site of colonization	No. (%) of patients		Infection rate[a]	RR (95% CI)	*P*
	All	Case patients			
Candida species					
In urine					
No	3649 (85)	25 (60)	0.79	—	
Yes	627 (15)	17 (40)	1.62	1.6 (0.9–3.1)	.13
In stool					
No	2996 (70)	16 (38)	0.70	—	
Yes	1280 (30)	26 (62)	1.34	1.4 (0.7–2.7)	.29
In both urine and stool					
No	3823 (89)	30 (71)	0.90	—	
Yes	453 (11)	12 (29)	1.35	1.1 (0.6–2.1)	.78
Candida albicans					
In stool					
No	2029 (71)	22 (58)	1.09	—	
Yes	820 (19)	16 (42)	1.25	1.0 (0.5–1.9)	.98
In urine					
No	3908 (91)	32 (76)	0.89	—	
Yes	368 (9)	10 (24)	1.59	1.4 (0.7–3.0)	.32

[a] Cases of candidal bloodstream infection per 1000 days in the surgical intensive care unit.

of subsequent CBSI was higher than for those who did not, but the difference did not reach statistical significance (1.62 vs. 0.79 CBSI per 1000 patient days; RR, 1.6; 95% CI, 0.9–3.1; $P = .13$). Recovery of *Candida* species from a rectal swab or from both a urine sample and a rectal swab was not associated with an increased risk of subsequently developing CBSI (table 6).

Multivariate analyses. In multivariate analyses of the entire cohort, factors independently associated with increased risk of CBSI included prior surgery (RR, 7.3; 95% CI, 1.0–53.8; $P = .05$), acute renal failure (RR, 4.2; 95% CI, 2.1–8.3; $P < .001$), and receipt of parenteral nutrition (RR, 3.6; 95% CI, 1.8–7.5; $P < .001$). Receipt of an antifungal agent was associated with a decreased risk of subsequent CBSI (RR, 0.3; 95% CI, 0.1–0.6; $P < .001$; table 7). A second multivariate model that included only patients who underwent surgery ($n = 3201$) identified an association between increased risk of CBSI and having had a triple-lumen catheter placed (RR, 5.4; 95% CI, 1.2–23.6; $P = .03$), in addition to the factors noted above. Having undergone neurosurgical or ear/nose/throat surgery was associated with decreased risk of subsequent CBSI (table 7). Receipt of an antifungal medication was significantly associated with decreased risk, as it was in the previous model.

Susceptibility testing and molecular typing. Antifungal susceptibility testing was performed on *Candida* isolates recovered from 35 of the 42 patients who developed a BSI (table 8). All isolates were susceptible to amphotericin B, 34 (97%) to flucytosine, and 31 (89%) were susceptible to fluconazole and itraconazole. Two of 8 *C. glabrata* isolates were resistant to fluconazole (MIC, ≥ 64 μg/mL), and 1 additional isolate demonstrated dose-dependent susceptibility (MICs, >8 μg/mL and <64 μg/mL). Two of 26 other *Candida* isolates (1 *C. albicans*

Table 7. Multivariate analyses of risk factors for candidal bloodstream infections in surgical intensive care unit (SICU) patients with and without prior surgery.

Model, risk factor	RR[a] (95% CI)	*P*
Model 1[b]		
Antifungal medication	0.3 (0.1–0.6)	<.001
Acute renal failure	4.2 (2.1–8.3)	<.001
Parenteral nutrition	3.6 (1.8–7.5)	<.001
Any surgery	7.3 (1.0–53.8)	.05
Model 2[c]		
Antifungal medication	0.2 (0.1–0.5)	<.001
Acute renal failure	3.8 (1.9–7.4)	<.001
Parenteral nutrition	2.8 (1.3–5.8)	.01
Neurological surgery	0.2 (0.04–0.7)	.02
Ear/nose/throat surgery	0.3 (0.1–0.9)	.02
Triple-lumen catheter	5.4 (1.2–23.6)	.03

[a] Adjusted for all of the factors listed under each model and for the admission hospital with use of proportional hazards regression.
[b] A total of 4276 SICU patients.
[c] A total of 3201 SICU patients who had prior surgery.

Table 8. In vitro antifungal susceptibility of *Candida* species isolates recovered from blood.

Isolate, antifungal agent tested	No. of isolates tested	MIC, μg/mL		
		Range	MIC_{50}	MIC_{90}
Candida albicans	16			
Amphotericin B		0.5–2.0	1.0	1.0
Flucytosine		0.12–2.0	0.25	2.0
Fluconazole		0.12–2.56	0.25	2.0
Itraconazole		0.015–16	0.03	0.25
Candida glabrata	8			
Amphotericin B		0.5–2.0	1.0	—
Flucytosine		0.06–0.5	0.25	—
Fluconazole		2.0–128	8.0	—
Itraconazole		0.012–16	1.0	—
Candida tropicalis	7			
Amphotericin B		0.5–1.0	1.0	—
Flucytosine		0.06–256	0.25	—
Fluconazole		0.25–256	0.5	—
Itraconazole		0.06–16	0.25	—
Candida parapsilosis	3			
Amphotericin B		0.5–1.0	1.0	—
Flucytosine		0.12–1.0	0.25	—
Fluconazole		0.5–256	1.0	—
Itraconazole		0.12–0.25	0.25	—
Candida lusitaniae	1			
Amphotericin B		1.0	—	—
Flucytosine		0.25	—	—
Fluconazole		1.0	—	—
Itraconazole		0.12	—	—

NOTE. National Committee for Clinical Laboratory Standards MIC break points [24] for susceptibility testing are as follows. Amphotericin B: no break point established. Flucytosine: susceptible, ⩽4 μg/mL; intermediate, 8–16 μg/mL; resistant, ⩾32 μg/mL. Fluconazole: susceptible, ⩽8 μg/mL; susceptible–dose dependent, 16–32 μg/mL; resistant, ⩾64 μg/mL. Itraconazole: susceptible, ⩽0.12 μg/mL; susceptible–dose dependent, 0.25–0.5 μg/mL; resistant, ⩾1 μg/mL.

and 1 *C. tropicalis*) were resistant to fluconazole (table 8). Molecular typing studies with use of pulsed-field gel electrophoresis, electrophoretic karyotyping, and (for *C. albicans*) a Ca3 probe were carried out on paired isolates from cultures of urine and blood samples from 18 patients whose urine cultures were positive for a *Candida* species before the onset of CBSI. Seventeen of 18 paired isolates had identical banding patterns.

DISCUSSION

The NEMIS SICU study is the largest prospective multicenter study to evaluate risk factors for the development of CBSI among SICU patients. There was a 6-fold variation in infection rates between institutions, from a low of 0.28 per 1000 patient-days to a high of 1.75 per 1000 patient-days. The 2 institutions with the highest rates of CBSIs are urban hospitals that care for large numbers of trauma patients. Previously reported data from the National Nosocomial Infections Surveillance (NNIS) system suggest that such patients have the greatest risk of developing nosocomial fungal infections [2, 3]. The fact that being a patient in the SICU at either of these institutions (in New York and Atlanta) was not independently associated with increased risk for development of CBSI in the multivariate analysis suggests that other risk factors accounted for the higher rate of CBSIs at those institutions.

It is interesting that ~25% of all patients admitted to an SICU did not undergo a surgical procedure. The risk of this subset of SICU patients developing a CBSI was clearly different than that of patients who underwent a surgical procedure. Patients who underwent a surgical procedure or had a CVC were ~11 times more likely to develop candidemia. Forty-one of the 42 CBSIs occurred in patients who had surgery and among those who had a CVC, with a rate of 1.2 per 1000 patient-days, versus 0.11 per 1000 patient-days for those who did not have a surgical procedure or a CVC.

In multivariate analyses, risk factors that were independently associated with increased risk of CBSI in our study included prior surgery (RR, 7.3), acute renal failure (RR, 4.2), and receipt of parenteral nutrition (RR, 3.6). Receipt of an antifungal drug significantly reduced the risk of developing a CBSI (RR, 0.3). When the model included only patients who underwent surgery, results were similar, but having had a triple-lumen catheter also proved to be a risk factor for developing CBSI (RR, 5.4). Our study helps further define the independent risk factors for CBSI in SICU patients and should help better identify high-risk patients in the SICU setting.

Potential risk factors for developing candidemia identified in previous studies have included receipt of antimicrobial agents, corticosteroids, chemotherapy, or parenteral therapy; hematological or solid organ malignancy; neutropenia; extensive surgery or burns; mechanical ventilation; a stay in an ICU (especially a surgical or neonatal ICU); an indwelling CVC or hemodialysis; and prior fungal colonization [2, 3, 6–11, 29, 30]. These studies have most frequently involved either patients with hematologic or solid organ malignancies exclusively or mixed patient populations [3]. Many of these previous studies have been limited by the fact that they often obtained data from a single institution or over a long period of time in order to ensure an adequate number of cases for review. In addition, few studies were prospective in design, and the few prospective studies have not focused on SICU populations. The large quantity of data and extent of data collection may account for the differences between our study and previous studies.

In our study, a high mortality rate (41%) was noted among patients who developed CBSIs, comparable to data from previous reports [3, 31–35]. Because of the high mortality rate

among patients who develop CBSIs, it has been suggested that prophylactic, presumptive, or empirical therapy be given to high-risk patients in the SICU [16, 17, 36, 37]. These strategies are frequently employed, and a number of institutions have developed algorithms for deciding whether to use antifungal therapy for at-risk patients who do not have a proven invasive candidal infection [16, 38–40]. Previous investigators reported the use of oral nystatin or ketoconazole [37], but recent recommendations have focused on the use of fluconazole [16]. However, how to identify high-risk patients has been incompletely defined and has varied in different reports; there are few data on the efficacy of antifungal prophylaxis or preemptive interventions for SICU patients.

The British Society for Antimicrobial Chemotherapy Working Party has recommended empirical therapy for high-risk patients who have a urine culture that is positive for *Candida* and who have a "deteriorating clinical status" [38], whereas other investigators have recommended presumptive therapy for any ICU patient who has fungal colonization [36]. Our finding that fungal colonization (of the urinary tract alone and/or rectum) does not have a high positive predictive value raises doubts about this approach.

Prophylactic use of fluconazole has been shown to reduce the incidence of invasive and superficial fungal infections among bone marrow transplantation patients in randomized controlled trials [39], but the emergence of infections due to natively resistant *Candida* species, such as *Candida krusei,* has been noted with fluconazole prophylaxis in this patient population [40]. Results of fluconazole prophylaxis among patients who have neutropenia and acute leukemia have been conflicting; one study showed no statistically significant reduction in invasive fungal infections [41], whereas a more recent study did show a significant reduction in invasive fungal infections [42]. Eggimann et al. [43] conducted a randomized, placebo-controlled trial to study the efficacy of fluconazole prophylaxis among 49 high-risk surgical patients with recurrent gastrointestinal perforations or anastomotic leakages. They reported that patients who received fluconazole were less likely to have abdominal colonization or infection (peritonitis) with *Candida* species, but they were unable to assess whether the prophylaxis affected the risk of acquiring a CBSI because of the small number of patients enrolled.

The finding in our study that receipt of an antifungal agent was associated with a reduced risk of developing CBSI for SICU patients is important and has not been reported from previous epidemiological investigations. In our study, the use of antifungal agents was determined by the physicians caring for the patients, and guidelines for antifungal use were neither provided nor part of the study protocol. A limitation of our study was that data on the specific type of azole drug used (e.g., fluconazole, ketoconazole, itraconazole, clotrimazole, or miconazole) were not recorded in the first year of the study. This limited our ability to further determine which antifungal drug (e.g., amphotericin B or a specific azole agent) was protective. Prospective clinical trials are needed to determine which high-risk patients would benefit from prophylaxis and which antifungal agents would be most useful.

Several authors have recommended performance of serial fungal surveillance cultures and initiation of presumptive antifungal therapy if any degree of fungal colonization is noted [17, 36], if patients are colonized at $\geqslant$2 sites, or if the colonization index is high [44] or candiduria is present in high-risk patients who are clinically unstable [38]. In our study, specimens of urine and rectal swabs for fungal surveillance culture were obtained on admission to the SICU and weekly thereafter. In 17 of 18 cases, molecular typing indicated that the colonizing strain was identical to the *Candida* isolate subsequently recovered from blood. Fungal colonization (defined as a urine or rectal swab culture positive for *Candida* species) was not associated with a statistically significant increase in risk of CBSI in univariate or multivariate analyses. Overall, 30% of the 4276 patients in the study had rectal colonization with a *Candida* species, 15% had urinary colonization, and 11% had both rectal and urinary colonization; however, only ~1% of the patients in the study developed a CBSI. The finding of urinary or rectal fungal colonization alone, as assessed in our study, does not appear to be clinically useful for deciding when to start presumptive antifungal therapy.

Other investigators [17] have suggested that an elevated APACHE II score can help identify high-risk ICU patients who should start receiving prophylactic or presumptive antifungal therapy, given the findings of a retrospective study reported by Fraser et al. [33] that an elevated APACHE II score was associated with increased risk of developing CBSI. In our prospective study, however, a higher APACHE II or McCabe and Jackson score on admission was not associated with a significantly higher risk of developing CBSI.

In summary, this report demonstrates that the wide variation in the rate of CBSI between institutions is likely due to the underlying risk factors of the different patient populations served by the geographically dispersed institutions, and it defines a number of risk factors that are independently associated with increased risk of CBSI. The finding that receipt of an antifungal drug is associated with a reduced risk of developing CBSI indicates the need for additional investigations to further define which high-risk patients should be given prophylactic or presumptive therapy and which antifungal agents are most beneficial.

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