ORIGINAL ARTICLE

Temporal Assessment of *Candida* Risk Factors in the Surgical Intensive Care Unit

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Hypothesis: Risk factors for *Candida* infection in surgical intensive care units (SICUs) change over time. Risk factor progression may influence *Candida* colonization and infection.

Design: Multicenter cohort survey.

Setting: Three urban teaching institutions.

Patients: A total of 301 consecutively admitted patients in SICUs for 5 or more days.

Main Outcome Measures: Assessment of patients on SICU days 1, 3, 4, 6, and 8 and SICU discharge for risk factors, *Candida* colonization, and antifungal use. *Candida* colonization status was categorized as noncolonized (NC), locally colonized (LC) if 1 site was involved, and disseminated infection (DI) if 2 or more sites or candidemia were involved.

Results: The most frequent risk factors in the 301 patients enrolled were presence of peripheral and central intravenous catheters, bladder catheters, mechanical ventilation, and lack of enteral or intravenous nutrition. Early risk factors included total parenteral nutrition or central catheter at SICU day 1 and previous SICU admissions or surgical procedures. Peak number of risk factors (mean ± SD) were as follows: 7.2 ± 2.6 in NC (n = 229), 9.2 ± 2.3 in LC (n = 45), and 9.2 ± 2.6 in DI (n = 27). These numbers were reached at day 8 in the NC and LC groups and day 4 in the DI group. The LC and DI groups had more risk factors on each SICU day than the NC group and longer median SICU length of stay (28 days in the DI group vs 11 and 19 days in the NC and LC groups, respectively). Antifungal therapy, while used most frequently in the DI group, was initiated later for this group than in NC and LC groups.

Conclusions: Risk factors for *Candida* infection in SICU patients change over time. Patients with DI demonstrate a greater number of and more rapid increase in risk factors than patients in the LC and NC groups. Presence of early risk factors at the time of SICU admission, a high incidence of risk factors, or a rapid increase in risk factors should prompt clinicians to obtain surveillance fungal cultures and consider empirical antifungal therapy.

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THE INCIDENCE of *Candida* bloodstream infections has increased during the past decade. In fact, *Candida* species is the fourth most common pathogen causing nosocomial bloodstream infection.[1] The incidence of candidemia has been shown to be higher in critical care units than other parts of the hospital. Despite numerous improvements in medical care during the past decade, disseminated *Candida* infections remain a major source of morbidity and mortality in the surgical intensive care unit (SICU).[2-9] Literature reports[2-7] have documented *Candida*-associated mortality rates that range from 30% to 57%. In addition, nosocomially acquired candidemia has been associated with a significant increase in length of stay.[3] Candidemia is, therefore, a significant economic and clinical burden to health care providers.[2] The cost associated with one episode of candidemia was recently estimated to be $34 123 to $44 536.[8] Management of disseminated *Candida* infections remains problematic because of difficulties in early detection and diagnosis of *Candida* infection. *Candida* is a frequent colonizer of the gastrointestinal tract, and the implication of isolation of *Candida* from various body fluids or sites is uncertain. Disseminated infection (DI), or visceral organ involvement, is frequently identified only during postmortem examination.[9-12] Clinicians, therefore, must rely on evaluation of risk factors to guide their identification of patients with the greatest probability of *Candida* infection.

See Invited Critique at end of article

Many investigators have attempted to characterize the association between the

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PATIENTS AND METHODS

STUDY DESIGN

This was a multicenter, prospective, observational cohort study conducted in 3 urban, level I trauma centers in the United States. Consecutive adult patients (>18 years of age) who remained in the SICU for 5 days or more were included. For the assessment of the relationship between risk and the outcome of colonization, patient cohorts were categorized by *Candida* colonization status as noncolonized (NC), locally colonized (LC) if 1 site was involved, or DI if 2 or more separate body sites were involved or if the patient had candidemia.[17] Investigational review board approval was obtained at all study sites before the start of data collection.

DATA COLLECTION AND PATIENT ASSESSMENTS

Complete patient assessments were performed prospectively on SICU days 1, 3, 4, 6, and 8 and on the date of discharge from the SICU. Data were collected at the time of assessment and entered on a laptop computer, using the Multiple Disease Risk Assessment Program (MDRA) developed by the Clinical Applications Team of Pfizer Inc, New York, NY (T.J.L., A.J.A.). The program allows entry of demographic data, comorbid conditions, risk factors, drug therapy, microbiology, and clinical and outcomes data. The MDRA was programmed to compute Acute Physiology and Chronic Health Evaluation II (APACHE II) scores from raw data at each time point evaluated. A unique feature of the program is the ability to collect data over time. Each patient assessment included age; sex; APACHE II score[18]; patient type, categorized as either trauma (penetrating or blunt) or surgery, which included neurologic, gastrointestinal (GI), orthopedic, head and neck, cardiothoracic, genital, integumentary, musculoskeletal, or respiratory; and risk factor evaluation. Each risk factor assessment consisted of determination of the presence or absence of a predefined list of risk factors for the development of *Candida* infection. The list of risk factors was chosen a priori by investigator consensus and based on risk factors most commonly reported in the literature.[5,13-17]

Risk Factors

Broad-spectrum antibiotics (providing gram-positive, gram-negative, and anaerobic coverage)
Use of 2 or more antibiotics
Hyperthermia (temperature >38.5°C) or hypothermia (temperature <36°C) while taking antibiotics
White blood cell count of more than 10000/μL or less than 1000/μL
Absolute lymphocyte count of less than 1000/μL
Serum creatinine level of more than 2 mg/dL (177 μmol/L)
Organ transplant
Current treatment for hematologic malignancy or solid tumor
Corticosteroid (nonphysiologic) use for more than 4 days
Severe burns
Diabetes mellitus
Hemodialysis
Presence of a central intravenous catheter
Placement of a central intravenous catheter for more than 72 hours
Presence of a peripheral intravenous catheter
Mechanical ventilation
Presence of a bladder catheter
Use of TPN
Lack of any enteral nutrition or TPN
GI surgery
Multiple surgical procedures or multiple SICU admissions within current admission
Transfer from another hospital
Diarrhea

Microbiologic data, including date, organism, and source, were collected on all fungal isolates from any body source and for any bacterial organism isolated from the blood. For all antifungal therapy used, data on the drug, dose, and duration and route of administration were collected. Outcome parameters were collected to document the presence or absence of *Candida* colonization or infection, all-cause SICU mortality, and length of stay in the SICU.

STATISTICAL ANALYSIS

Patients in the LC and DI groups were compared with patients in the NC group to describe risk of colonization or infection by SICU day. Based on low numbers in the DI group, a post hoc analysis was performed to compare patients in the LC and DI groups collectively with NC patients. Univariate analyses were performed using the Pearson χ^2 test for categorical data. Continuous data were evaluated using a 2-tailed *t* test for equality of means and a post hoc Scheffé test for multiple comparisons. The relationship of changing risk factors and time was studied using mean changes from day to day. Because of the short series, which included only 6 assessments, it was determined that time-series analysis was not appropriate. Multiple logistic regression analysis was conducted to predict *Candida* colonization status. Several models were built using either all risk factors or only those found to be significant in univariate analysis. Models were created for each assessment day, and each was tested using sensitivity and specificity analyses. A computer program (Microsoft Access; Microsoft, Seattle, Wash) was used to run the preliminary analysis, and statistical software (SPSS version 10.0; SPSS Inc, Chicago, Ill) was used to conduct all statistical analyses. $P \leq .05$ was considered significant for all analyses.

presence of various risk factors and the incidence of *Candida* infections.[5,13-17] Risk factors that have been identified in these reports are numerous and include burns, total parenteral nutrition (TPN), diabetes mellitus, leukopenia, gastrointestinal disease or surgery, prior treatment with antibiotics, the number of antibiotics prescribed, catheterization, end-organ disease, transfer from another hospital, malignancy, bladder catheterization, hemodialysis, diarrhea, *Candida* colonization, and length of time in the SICU.[3,5,13-17] The results of these analyses are limited in that these studies are often retrospective in nature, assess patients at a single point in time, and do not differentiate between various subtypes of critically ill patients. Although individual risk factors have been evaluated to predict *Candida* infection, characterization of the progression of risk factors has not been described to our knowledge and may provide clinicians with a greater ability to identify the circumstance when patients are at the greatest risk for fungal infections. Earlier identification of these at-risk patients will enable clinicians to increase fungal surveillance efforts. Empirical an-

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Table 1. Demographics

Demographic*	Group: Noncolonized (n = 229)	Locally Colonized (n = 45)	Disseminated Infection (n = 27)	Total (N = 301)
Age, mean ± SD, y	50.4 ± 18.9	50.2 ± 16.4	54.3 ± 17.3	50.7 ± 18.4
APACHE II score (day 1), mean ± SD	18.6 ± 9.8	19.5 ± 7.9	18.5 ± 8.1	18.7 ± 9.4
Patient type, % (No./total No.)				
Blunt trauma	70 (49/71)	25 (18/71)	6 (4/71)	24 (71/301)
Gastrointestinal surgery	66 (37/56)	18 (10/56)	16 (9/56)	19 (56/301)
Cardiothoracic	78 (32/41)	15 (6/41)	7 (3/41)	14 (41/301)
Neurological surgery	80 (32/40)	15 (6/40)	5 (2/40)	13 (40/301)
Head and neck	80 (24/30)	3 (1/30)	16 (5/30)	10 (30/301)
Penetrating trauma	84 (21/25)	8 (2/25)	8 (2/25)	8 (25/301)
Orthopedic surgery	91 (10/11)	9 (1/11)	0 (0/11)	4 (11/301)
Other surgery	85 (23/27)	7 (2/27)	7 (2/27)	9 (27/301)

*APACHE II indicates Acute Physiology and Chronic Health Evaluation II; other surgery, genital, integumentary, or musculoskeletal surgery.

tifungal therapy can then be considered as a potential means to reduce morbidity and mortality associated with disseminated *Candida* disease. The goals of this study are to evaluate the incidence and progression of risk factors over time and to assess the relationship between risk factor progression and *Candida* colonization or infection in the SICU.

RESULTS

PATIENT CHARACTERISTICS

A total of 301 consecutively treated SICU patients were enrolled at 3 different US health centers: Detroit Receiving Hospital, Detroit, Mich (n=101), The Ohio State University Medical Center, Columbus (n=100), and Los Angeles County University of Southern California Medical Center, Los Angeles (n=100). Patients were enrolled from August 1999 to February 2000. Results are presented as mean±SD. Overall, the mean age was 50.7±18.4 years, and the mean APACHE II score was 18.7±9.4. Patients with blunt trauma and those undergoing GI surgery comprised the largest patient groups. Patient demographics and the distribution of patient types were analyzed for each *Candida* colonization group (NC, LC, and DI) and are given in **Table 1**. The progression of APACHE II scores as assessed on days 1, 3, 4, 6, and 8 and at discharge from the SICU according to colonization status is illustrated in **Figure 1**. APACHE II scores were significantly greater in the LC and DI groups compared with the NC group on days 3 (P=.004), 4 (P=.003), and 6 (P=.002).

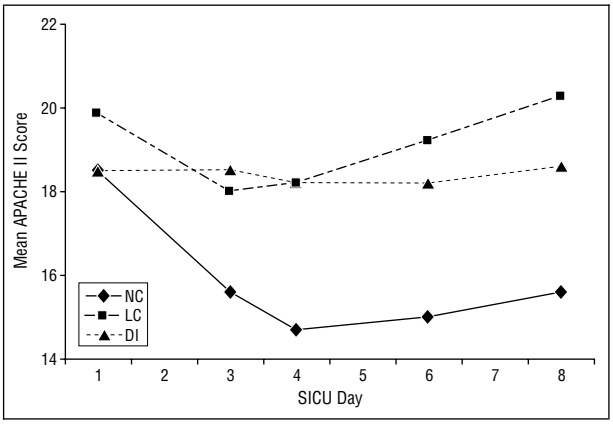

Figure 1. Acute Physiology and Chronic Health Evaluation II (APACHE II) score by surgical intensive care unit (SICU) day. Differences were statistically significant on days 3 (P=.004), 4 (P=.003), and 6 (P=.002). NC indicates noncolonized; LC, locally colonized; and DI, disseminated infection.

RISK FACTOR ASSESSMENTS

Total numbers of risk factors per day averaged for assessment days 1 through 8 were 8.5±2.3, 8.7±2.4, and 6.8±2.4 for the LC, DI, and NC groups, respectively. As illustrated in **Figure 2**, NC patients had significantly fewer risk factors present on each assessment day than LC and DI patients (P<.01). This difference remained significant even when patients who died were removed from the analysis. The most frequently occurring risk factors for each SICU day, in order of prevalence on SICU day 1 and evaluated separately for each colonization group, are presented in **Table 2**. Risk factors seen in the greatest number of patients include presence of an intravenous (peripheral and central) or bladder catheter, mechanical ventilation, leukocytosis, and broad spectrum antibiotic use. The *Candida* risk factors found to be most

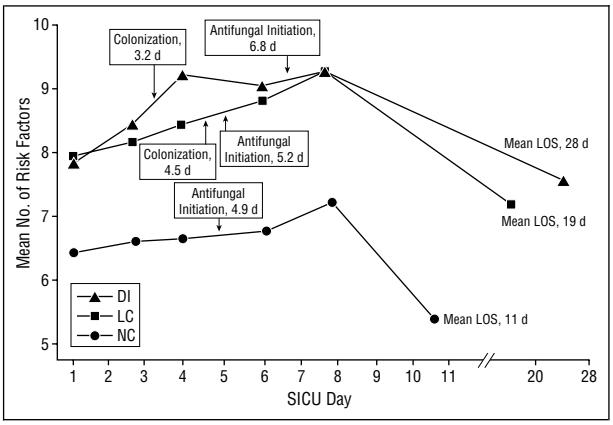

Figure 2. Risk factor progression by *Candida* colonization group. NC indicates noncolonized; LC, locally colonized; DI, disseminated infection; LOS, length of stay; and SICU, surgical intensive care unit.

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Table 2. Most Common Risk Factors by Surgical Intensive Care Unit Day Within Each *Candida* Colonization Group*

	Day					
	1			3		
Risk Factor	NC (n = 229)	LC (n = 45)	DI (n = 27)	NC (n = 229)	LC (n = 45)	DI (n = 27)
Bladder catheter	212 (92.6)	45 (100)	27 (100)	216 (94.3)	45 (100)	26 (96.3)
Peripheral catheter	199 (86.9)	36 (80.0)	20 (74.1)	183 (79.9)	35 (77.8)	15 (55.6)
Lack of enteral or intravenous feeding	180 (78.6)	38 (84.4)	23 (85.2)	152 (66.4)	37 (82.2)	18 (66.7)
Mechanical ventilation	168 (73.4)	36 (80.0)	22 (81.5)	**158 (69.0)**	**38 (84.4)**	**23 (85.2)**
Central catheter	**158 (69.0)**	**36 (80.0)**	**25 (92.6)**	173 (75.5)	37 (82.2)	25 (92.6)
White blood cell count >10 000/μL	127 (55.5)	32 (71.1)	15 (55.6)	129 (56.3)	24 (53.3)	17 (63.0)
Broad spectrum antibiotics	85 (37.1)	22 (48.9)	8 (29.6)	97 (42.4)	22 (48.9)	15 (55.6)
Gastrointestinal surgery	57 (24.9)	13 (28.9)	11 (40.7)	53 (23.1)	13 (28.9)	11 (40.7)
Multiple surgical procedures	45 (19.7)	16 (35.6)	11 (40.7)	45 (19.7)	16 (35.6)	11 (40.7)
Central catheter >72 h	43 (18.8)	18 (40.0)	9 (33.3)	62 (27.1)	19 (42.2)	10 (37.0)
Fever or hypothermia	50 (21.8)	15 (33.3)	5 (18.5)	62 (27.1)	19 (42.2)	9 (33.3)
Transfer from other hospital	39 (17.0)	7 (15.6)	9 (33.3)	37 (16.2)	7 (15.6)	9 (33.3)
Diabetes mellitus	30 (13.1)	7 (15.6)	8 (29.6)	30 (13.1)	7 (15.6)	8 (29.6)
Solid tumor	18 (7.9)	5 (11.1)	4 (14.8)	18 (7.9)	5 (11.1)	4 (14.8)
>2 Antibiotics	18 (7.9)	4 (8.9)	3 (11.1)	24 (10.5)	7 (15.6)	5 (18.5)
Serum creatinine level >2 mg/dL	18 (7.9)	3 (6.7)	2 (7.4)	22 (9.6)	6 (13.3)	5 (18.5)
Total parenteral nutrition	**16 (7.0)**	**7 (15.6)**	**3 (11.1)**	**36 (15.7)**	**12 (26.7)**	**8 (29.6)**
Multiple intensive care unit stays	**11 (4.8)**	**5 (11.1)**	**3 (11.1)**	**10 (4.4)**	**5 (11.1)**	**3 (11.1)**
Hemodialysis	3 (1.3)	3 (6.7)	0	5 (2.2)	3 (6.7)	1 (3.7)
Diarrhea	**1 (0.4)**	**3 (6.7)**	**2 (7.4)**	5 (2.2)	3 (6.7)	1 (3.7)

*Factors found to be significantly different between groups for each day are given in boldface type. NC indicates noncolonized; LC, locally colonized; and DI, disseminated infection. All data are given as number (percentage).

prevalent for each assessment day differed during the time that patients remained in the SICU. For example, although use of broad spectrum antibiotics and TPN increased over time, the numbers of patients with peripheral catheters or central catheters and those not receiving either enteral or parenteral feeding decreased.

The results from the univariate analysis identified those risk factors independently related to *Candida* colonization or infection for each assessment day. The risk factors found to be significantly associated with colonization or infection are listed with their corresponding odds ratios in **Table 3**. Factors associated with colonization or infection were deemed to be either early risk factors (present at SICU admission or by day 3) or late risk factors (present by days 4-8). Early risk factors included diarrhea, TPN, multiple SICU admissions or multiple surgical procedures, mechanical ventilation, and presence of a central catheter or presence of a central catheter that was in place for longer than 72 hours. Late risk factors included hemodialysis, persistent leukocytosis, fever or hypothermia while taking antibiotics, use of broad-spectrum antibiotics, solid tumor, and lack of nutritional support.

Multivariate analysis using logistic regression identified that on day 1 use of a central catheter for more than 72 hours, multiple surgical procedures, and diarrhea were independent and significant predictors of colonization and DI. On day 3, presence of a peripheral catheter and use of a central catheter for more than 72 hours and use of mechanical ventilation on day 4 were significant predictors. Model sensitivity was 0.3, 0.22, and 0.32, and specificity was 0.96, 0.95, and 0.96 for days 1, 2, and 3, respectively. Although specificity is adequate, the sensitivity results are likely owing to the relatively low numbers in the LC and DI groups and the unequal distribution between patients with colonization and NC groups.

CANDIDA COLONIZATION AND INFECTION

In both the LC and DI groups, the most commonly isolated species was *Candida albicans*, occurring in 43.2% of all isolates. This was followed by *Candida glabrata*, which occurred in 13.1% of isolates; other non–*C albicans* species were identified in only 4.3% of cases. All other isolates were identified as *Candida* organisms. The body sites most frequently involved were respiratory, surgical wound, urinary tract, and blood. Most patients in the DI group had more than 1 site positive for *Candida* infection: 20 patients had 2 sites positive; 4, 3 sites; and 2, 4 sites. Six DI patients had *Candida* organisms isolated from the blood. The mean number of SICU days before the identification of candidemia was 9.27±5.6. In 4 of these 6 patients, the blood culture was the first culture positive for *Candida* obtained in the SICU. In the other 2 patients, the positive blood culture was preceded by multiple other cultures positive for fungi. Patients within LC or DI groups had a significantly greater likelihood of having bacteremia (39.1% and 48.4%, respectively) than did NC patients (19.7%) ($P<.01$).

ANTIFUNGAL THERAPY

Characteristics of the antifungal therapy used in the study cohort are summarized in **Table 4**. The most frequently used local therapies included nystatin "swish and swallow" or topical azole antifungals. Use of systemic therapy was infrequent in the NC group. This is in con-

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4			6			8		
NC (n = 229)	LC (n = 45)	DI (n = 27)	NC (n = 165)	LC (n = 39)	DI (n = 26)	NC (n = 110)	LC (n = 36)	DI (n = 24)
213 (93.0)	45 (100)	27 (100)	151 (91.5)	39 (100)	26 (100)	102 (92.7)	36 (100)	24 (100)
170 (74.2)	31 (68.9)	15 (55.6)	125 (75.8)	26 (66.7)	15 (57.7)	80 (72.7)	21 (58.3)	13 (54.2)
133 (58.1)	34 (75.6)	17 (63.0)	**81 (49.1)**	**31 (79.5)**	**15 (57.7)**	60 (54.5)	23 (63.9)	14 (58.3)
134 (58.5)	**36 (80.0)**	**24 (88.9)**	**106 (64.2)**	**31 (79.5)**	**22 (84.6)**	**77 (70.0)**	**32 (88.9)**	**22 (91.7)**
163 (71.2)	**39 (86.7)**	**24 (88.9)**	**110 (66.7)**	**30 (76.9)**	**23 (88.5)**	**62 (56.4)**	**28 (77.8)**	**21 (87.5)**
115 (50.2)	**29 (64.4)**	**21 (77.8)**	**90 (54.5)**	**29 (74.4)**	**17 (65.4)**	**65 (59.1)**	**33 (91.7)**	**18 (75.0)**
99 (43.2)	**25 (55.6)**	**16 (59.3)**	**80 (48.5)**	**27 (69.2)**	**17 (65.4)**	**70 (63.6)**	**31 (86.1)**	**18 (75.0)**
52 (22.7)	13 (28.9)	11 (40.7)	39 (23.6)	12 (30.8)	11 (42.3)	28 (25.5)	11 (30.6)	9 (37.5)
44 (19.2)	**16 (35.6)**	**11 (40.7)**	**37 (22.4)**	**15 (38.5)**	**11 (42.3)**	30 (27.3)	14 (38.9)	10 (41.7)
136 (59.4)	28 (62.2)	23 (85.2)	94 (57.0)	23 (59.0)	23 (88.5)	57 (51.8)	21 (58.3)	9 (37.5)
59 (25.8)	**18 (40.0)**	**12 (44.4)**	36 (21.8)	14 (35.9)	6 (23.1)	46 (41.8)	21 (58.3)	7 (29.2)
37 (16.2)	7 (15.6)	9 (33.3)	26 (15.8)	6 (15.4)	9 (34.6)	13 (11.8)	6 (16.7)	8 (33.3)
30 (13.1)	7 (15.6)	8 (29.6)	25 (15.2)	7 (17.9)	8 (30.8)	15 (13.6)	7 (19.4)	8 (33.3)
18 (7.9)	5 (11.1)	4 (14.8)	**8 (4.8)**	**5 (12.8)**	**4 (15.4)**	**4 (3.6)**	**4 (11.1)**	**2 (8.3)**
25 (10.9)	7 (15.6)	6 (22.2)	21 (12.7)	8 (20.5)	6 (23.1)	15 (13.6)	7 (19.4)	5 (20.8)
24 (10.5)	7 (15.6)	4 (14.8)	18 (10.9)	5 (12.8)	3 (11.5)	11 (10.0)	5 (13.9)	4 (16.7)
49 (21.4)	**17 (37.8)**	**9 (33.3)**	53 (32.1)	19 (48.7)	10 (38.5)	40 (36.4)	19 (52.8)	13 (54.2)
10 (4.4)	**5 (11.1)**	**3 (11.1)**	8 (4.8)	4 (10.3)	3 (11.5)	5 (4.5)	3 (8.3)	2 (8.3)
3 (1.3)	**3 (6.7)**	**2 (7.4)**	2 (1.2)	3 (7.7)	1 (3.8)	**1 (0.9)**	**3 (8.3)**	**2 (8.3)**
4 (1.7)	2 (4.4)	0	4 (2.4)	0	1 (3.8)	3 (2.7)	3 (8.3)	1 (4.2)

Table 3. Association Between *Candida* Risk Factors and Colonization or Infection During Surgical Intensive Care Unit Stay*

	Day				
Risk Factor, OR	**1**	**3**	**4**	**6**	**8**
Diarrhea	17.02	. . .	. . .	. . .	. . .
Total parenteral nutrition	3.19	2.06	2.08	. . .	. . .
Multiple intensive care unit admissions	2.74	3.13	2.74	. . .	. . .
Central catheter >72 h	2.60	1.82	. . .	. . .	. . .
Multiple surgical procedures	2.49	2.31	2.52	2.31	. . .
Central catheter	2.49	. . .	2.83	2.21	3.45
Mechanical ventilation	. . .	2.49	3.55	2.46	3.86
Hemodialysis	. . .	. . .	5.62	. . .	9.90
White blood cell count >10 000/μL	. . .	. . .	2.25	2.02	3.92
Fever or hypothermia	. . .	. . .	2.06	. . .	. . .
Broad spectrum antibiotics	. . .	. . .	1.74	2.26	2.55
Solid tumor	. . .	. . .	. . .	3.16	2.00
Lack of enteral or intravenous nutrition	. . .	. . .	. . .	2.51	. . .

*Odds ratios (ORs) for variables found to be significant by univariate analysis of association. Risk factors and the corresponding ORs are listed in chronological order of appearance, eg, those factors identified to be significantly related to infection early in the surgical intensive care unit stay are listed first, whereas those factors not reaching significance until late in the surgical intensive care unit stay are listed last. Ellipses indicate not significant.

trast to the LC and DI groups, in which approximately 50% and 85% of patients, respectively, received systemic antifungal therapy. Patients in the LC group received systemic antifungal therapy approximately 1 day earlier on average than did DI patients. The duration of systemic antifungal therapy averaged from 10 to 14 days and was shorter in the NC group than in the LC or DI groups. The most frequently used systemic agents were fluconazole and amphotericin B. In 6 of 13 patients receiving an amphotericin B product systemically, a lipid formulation was used. Dosing of amphotericin B ranged from 0.5 to 1.0 mg/kg daily, and when the lipid formulation was used, it was administered at 5 mg/kg in all instances. The most commonly used daily dose of fluconazole was 400 mg/d.

RELATIONSHIPS AMONG RISK FACTORS, *CANDIDA* COLONIZATION STATUS, AND ANTIFUNGAL USE

The risk factor progression throughout SICU admission in relation to the initiation of antifungal therapy is pre-

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Table 4. Antifungal Use

Variable	Group: Noncolonized (n = 229)	Locally Colonized (n = 45)	Disseminated Infection (n = 27)
Local antifungal, %*	5.2	6.7	29.6
Systemic antifungal (SAF), %*	10.9	51.1	85.2
Time to initiate SAF, mean ± SD, d	4.6 ± 3.3	5.7 ± 5.8	6.8 ± 5.8
Duration of SAF, mean ± SD, d	9.8 ± 10.4	14.0 ± 11.0	13.9 ± 12.3

*Groups significantly different at $P<.05$.

Table 5. Clinical Characteristics and Outcomes*

	Surgical Intensive Care Unit Length of Stay, Mean ± SD, d	Mortality, %
Colonization status		
Noncolonized group (n = 229)	11.2 ± 7.5†	8.3
Locally colonized group (n = 45)	19.1 ± 13.1†	25.0
Disseminated infection group (n = 27)	28.1 ± 22.0†	14.8
Total (N = 301)	13.9 ± 11.7	11.4

*The F or χ^2 statistic was significant for the surgical intensive care unit length of stay (37.45) and for mortality (10.55).
†Groups significantly different at $P<.05$.

sented for each colonization group in Figure 2. The number of risk factors differed significantly on each SICU day between the NC and both the LC and DI groups. The mean time to reach the peak number of risk factors was significantly shorter in the LC and DI groups when compared with NC patients. Patients with DI demonstrated the most rapid increase in the number of risk factors, reaching more than 9 risk factors by day 4 in the SICU. Within the DI group, there was a significant increase in the number of risk factors between days 1 and 3 ($P=.03$) and between days 3 and 4 ($P=.002$). The average number of risk factors detected in NC patients was less than 7 for all but day 8. Patients in the DI group demonstrated significantly more risk factors than NC patients, because on no days do the 95% confidence intervals for the mean number of risk factors between DI and NC overlap. Antifungal therapy was initiated earliest in the NC group and latest in the DI group, as illustrated in Figure 2 and Table 4.

CLINICAL CHARACTERISTICS AND OUTCOMES

Overall SICU mortality in the study population was 11.4%. Patients with either blunt trauma or those undergoing GI surgery demonstrated the greatest overall SICU mortality (26.5% and 29.4%, respectively) and the longest SICU length of stay (>15 days). Length of stay in the SICU and all-cause SICU mortality in relation to *Candida* colonization status are given in **Table 5**. A significantly shorter SICU length of stay was noted in the NC group compared with the LC or DI group. Patients in the DI group experienced a mean length of stay of 28.1 days, more than twice that observed in the NC group and significantly longer than the SICU stay (19.1 days) for patients in the LC group ($P<.001$).

COMMENT

Early detection and diagnosis of *Candida* infection is problematic, and the mortality and cost related to its management remain high.[2,8,19] The persistent increase in *Candida* infection during the past 2 decades has prompted numerous efforts to characterize risk factors that can accurately predict *Candida* infections. Although numerous studies[5,11-17] have evaluated risk factors for candidemia using various univariate and multivariate techniques, several methodologic limitations restrict the extrapolation of these results to SICU clinical practice. Determining the change in *Candida* risk factors over time is potentially more clinically relevant than evaluating risk factors at any given point in time. In the present study, we have not only characterized risk factors contributing to *Candida* colonization and infection but also evaluated how these risk factors change during an SICU stay. Throughout the SICU stay, the absolute number and peak number of risk factors were always greater in LC or DI patients than in the NC group. Patients with DI were found to have a greater number of risk factors present and to have different risk factors present at different times throughout the study period. In addition, the present data describe a more rapid increase in the progression of risk factors in DI patients. In contrast, there was a slower and smaller increase in the number of risk factors identified in the NC patients. Patients with a rapid increase in risk factors owing to short-term exposure to more invasive procedures and those demonstrating clinical deterioration during the SICU stay are more likely to be in the LC and DI groups. This provides clinicians with a means to prospectively identify patients at high risk for *Candida* infections, not only from the number of risk factors on any given day but also based on the changes in these risk factors from the time of SICU admission.

The specific risk factors found to have the greatest association with either colonization or infection varied during the SICU admission. Early in the SICU stay, similarities were noted between all colonization groups in terms of the numbers of certain risk factors present, particularly those risk factors that may be common to most patients in the immediate postoperative period. Similar numbers of patients within each group have elevations in white blood cell counts and fever or hypothermia and many receive broad spectrum antibiotics beginning on SICU day 1. Early on, these factors cannot provide a distinction between NC patients and those who will have *Candida* colonization or infection. However, several early risk factors were identified and were found to be significantly related to colonization or infection by SICU days 1 through 3. The presence of these risk factors may help the SICU clinician discriminate between patients with colonization and NC patients as early as day 1. These early risk factors, such as multiple SICU admissions or mul-

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tiple surgical procedures, the use of TPN, and the presence of central catheters, particularly if in place for longer than 72 hours, when present on day 1, indicate a greater early risk of *Candida* colonization or infection. This is in contrast to some previous studies that characterized the most significant risk factors as those tending to occur later in the SICU stay.[2,10,15,16] These include persistence of fever (or hypothermia) or leukocytosis in the face of antibiotic therapy, continued requirement for mechanical ventilation, and/or broad spectrum antibiotics. In clinical practice, it is frequently interpreted that patients with lack of improvement by day 4 may be at increased risk for fungal infection.[2] In fact, at all 3 institutions participating in the present study, guidelines for the use of empirical antifungal therapy include a provision for use in surgical patients with lack of improvement in clinical signs and symptoms of infection despite antibiotic therapy when assessed at 96 hours. In our study, these risk factors did not identify patients at risk until days 4 through 8. Knowledge of those risk factors that represent earlier risk of colonization or infection should improve our ability to identify patients likely to benefit from empirical therapy. It must also be considered that the course of progression of both early and late risk may be compounded in any given patient during the SICU stay.

Another assessment of change in clinical status over time involved evaluation of APACHE II scores. In the present study, APACHE II scores in LC and DI patients remain high and similar to baseline values, whereas NC patients show a significant reduction in APACHE II scores by day 3. It must be noted, however, that many of the identified risk factors are also components of the APACHE II score and that some of these components are affected by the presence of infection. Differentiation between a risk factor for infection and a response that results from infection may be difficult. Two studies performed in critically ill surgical patients have reported that high APACHE II scores are predictive of disseminated *Candida* infection. Nassoura et al[10] reported APACHE II scores of 14.1±3.2 in patients with DI compared with 5.0±4.6 in patients with candiduria who did not develop DI. Similarly, Pittet et al[11] reported that high APACHE II scores were predictive of dissemination. In their study, patients with *Candida* colonization had mean APACHE II scores of 17 compared with 28 in those patients with DI. However, the progression of APACHE II scores has not been evaluated over time. In our analysis of critically ill surgery patients, initial APACHE II scores were similar between colonization groups, averaging 18.7±9.4; however, these scores diverged between groups over time. APACHE II scores remained greater than 18 throughout the SICU stay in patients with colonization and infection, whereas the scores for NC patients decreased significantly from baseline by SICU day 3. Improvement in APACHE II scores by SICU day 3 was negatively correlated with colonization or infection in our study.

Algorithms for empirical treatment of *Candida* infections frequently include some combination of risk factors in addition to lack of response to antibiotics, usually reflected in persistent elevation of temperature or white blood cell count.[2,10] Often *Candida* colonization at more than 2 or 3 sites is used to guide treatment.[10,15,16] Another variable described by Nolla-Salas et al[20] includes the total number of predisposing risk factors for invasive *Candida* disease that are present in a given patient. These authors reported that of patients with candidemia, all patients had more than 1 risk factor, and the median number of predisposing risk factors was 8 (range, 2-12). This is similar to the findings of the present study. We report a mean of 8 to 9 risk factors present throughout the SICU stay in LC or DI patients, whereas NC patients consistently had risk factors numbering, on average, less than 7.

When evaluating the potential benefit of early antifungal therapy, it is essential to identify those patients at highest risk and the time at which the greatest risk of developing *Candida* infection occurs. Prophylactic fluconazole therapy has been compared with placebo in high-risk surgical and trauma patients. Ables et al[21] evaluated 119 trauma, intra-abdominal, or intrathoracic surgical patients with an anticipated SICU stay of more than 48 hours and 1 or more risk factors and showed no benefit of fluconazole therapy in preventing *Candida* infection. It is possible that inclusion of patients with a relatively low risk of *Candida* infection could mask the potential benefit likely in higher-risk patients. In contrast, Eggimann et al[15] demonstrated a significant benefit in a well-matched group of high-risk critically ill surgical patients. These patients had had recent abdominal surgery and either recurrent gastrointestinal perforations or anastomotic leaks and had undergone a median of 2 or more surgical interventions. *Candida* peritonitis was reduced, and a trend toward a reduced length of stay was observed in the fluconazole-treated patients. This study was effective in demonstrating the benefits of prophylaxis because these patients were of sufficiently high risk to benefit from antifungal therapy. Our study design allowed inclusion of some patient types, such as head and neck and genitourinary surgery, who demonstrated relatively low numbers of risk factors and low rates of *Candida* colonization or infection. Exclusion of such patient types increases the underlying incidence of *Candida* colonization and infection and provides greater ability to identify those patients at risk. Future studies designed to evaluate the potential benefit of empirical antifungal therapy will be more likely to be able to detect an impact of therapeutic intervention if only patients at high risk are included.

A limitation of the present study is that although data were obtained for all fungal cultures collected in the SICU, there was no systematic surveillance mandated by the study protocol. Accordingly, patients with *Candida* colonization may have been misclassified as NC if colonization was present but not detected. By using routine culture data, our study is reflective of a real-world scenario, evaluating data that a clinician would routinely have available for patient assessment. Future studies may benefit from aggressive surveillance obtaining culture specimens from multiple sites to more precisely classify patients as having colonization or infection. Other limitations include the fact that patients were assessed only during their SICU stay. In patients who were transferred to the SICU from another hospital ward, data on

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risk factors, fungal cultures, and therapy preceding their SICU admission were not collected. Also, mortality was assessed only during the SICU admission, and there was no attempt made to evaluate mortality specifically attributable to *Candida* infection.

CONCLUSIONS

This study is the first, to our knowledge, to characterize the progression of *Candida* risk factors during a patient's stay in the SICU. Patients who develop either local *Candida* colonization or DI have significantly different risk factor profiles than NC patients. Early risk factors, such as multiple SICU admissions or multiple surgical procedures, use of TPN, or presence of a central catheter that has been in place for longer than 72 hours, may already be evident at SICU day 1. These early markers should be considered by clinicians and used in concert with the progression of risk factors such as fever and white blood cell count, duration of broad-spectrum antibiotic use, and mechanical ventilation that may occur later. Such information allows clinicians to assess the *Candida* risk on a continual basis during the SICU stay, rather than waiting until day 4 to assess fungal risk. Ideally, the early identification of patients who may develop *Candida* infection can be used to interrupt the progression from *Candida* colonization to infection and decrease morbidity and mortality. In those SICU patients with early risk factors at day 1, more than 8 risk factors at any time, an APACHE II score greater than 18 by day 3 or 4, and/or those with rapidly changing risk factors, surveillance fungal cultures should be routinely obtained and empirical antifungal therapy considered. Studies designed to demonstrate the benefit of empirical antifungal therapy need to assess high-risk patients at the time of greatest risk and initiate therapy early enough in the disease to interrupt the progression from LC to DI.

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REFERENCES

1. Jones RN, Marshall SA, Pfaller MA, et al. Nosocomial enterococcal blood stream infections in the SCOPE program: antimicrobial resistance, species occurrence, molecular testing results, and laboratory testing accuracy. *Diagn Microbiol Infect Dis.* 1997;29:95-102.
2. Goff DA, Sierawski SJ, Fass RJ. Cost analysis of *Candida* infection among surgical intensive care unit patients. *Clin Drug Invest.* 1996;12:176-180.
3. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Hospital-acquired candidemia: the attributable mortality and excess length of stay. *Arch Intern Med.* 1988;148:2642-2645.
4. Eubanks PJ, Virgilio C, Klein S, Bongard F. *Candida* sepsis in surgical patients. *Am J Surg.* 1993;166:617-620.
5. Fraser J, Jones M, Dunkel J, Medoof G, Dunagan WC. Candidemia in a tertiary care hospital: epidemiology, risk factors and predictors of mortality. *Clin Infect Dis.* 1992;15:414-421.
6. Voss A, Noble JL, Verduyn L, Foudraine NA, Meis JF. Candidemia in intensive care unit patients: risk factors for mortality. *Infection.* 1997;25:8-11.
7. Karlowsky JA, Zhanel GG, Klym KA, Hoban DJ, Kabani AM. Candidemia in a Canadian tertiary care hospital from 1976-1996. *Diagn Microbiol Infect Dis.* 1997; 29:5-9.
8. Rentz AM, Halpern MT, Bowden R. The impact of candidemia on length of hospital stay, outcome, and overall cost of illness. *Clin Infect Dis.* 1998;27:781-788.
9. Wenzel RP. Nosocomial candidemia: risk factors and attributable mortality. *Clin Infect Dis.* 1995;20:1531-1534.
10. Nassoura Z, Ivatury RR, Simon RJ, Jabbour N, Stahl WM. Candiduria as an early marker of disseminated infection in critically ill surgical patients: the role of fluconazole therapy. *J Trauma.* 1993;35:290-295.
11. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. *Candida* colonization and subsequent infection in critically ill surgical patients. *Ann Surg.* 1994;220:751-758.
12. Hughes WT. Systemic candidiasis: a study of 109 fatal cases. *Pediatr Infect Dis.* 1982;1:11-18.
13. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Risk factors for hospital acquired candidemia: a matched case-control study. *Arch Intern Med.* 1989;149: 2349-2353.
14. Talbot BJ, Maislin GH, Hurwitz S, Strom BL. Risk factors for nosocomial candidemia: a case control study in adults without leukemia. *Am J Med.* 1989;87:614-620.
15. Eggimann P, Francioli P, Bille J, et al. Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients. *Crit Care Med.* 1999;27: 1066-1072.
16. Borzotta AP, Beardsley K. *Candida* infections in critically ill trauma patients: a retrospective case-control study. *Arch Surg.* 1999;134:657-665.
17. Cornwell EE, Blezberg H, Berne TV, et al. The pattern of fungal infections in critically ill surgical patients. *Am Surg.* 1995;61:847-850.
18. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985;13:818-829.
19. Edwards JE. Invasive *Candida* infections: evolution of a pathogen. *N Engl J Med.* 1991;324:1060-1062.
20. Nolla-Salas J, Sitges-Serra A, Leon-Gil C, et al. Candidemia in non-neutropenic critically ill patients: analysis of prognostic factors and assessment of systemic antifungal therapy. *Intensive Care Med.* 1997;23:23-30.
21. Ables AZ, Blumer NA, Valainis GT, et al. Fluconazole prophylaxis of severe *Candida* infection in trauma and postsurgical patients: a prospective, double-blind randomized, placebo-controlled trial. *Infect Dis Clin Pract.* 2000;9:169-175.

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