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# *Candida* Colonization and Subsequent Infections in Critically Ill Surgical Patients

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## Objective
The authors determined the role of *Candida* colonization in the development of subsequent infection in critically ill patients.

## Design
A 6-month prospective cohort study was given to patients admitted to the surgical and neonatal intensive care units in a 1600-bed university medical center.

## Methods
Patients having predetermined criteria for significant *Candida* colonization revealed by routine microbiologic surveillance cultures at different body sites were eligible for the study. Risk factors for *Candida* infection were recorded. A *Candida* colonization index was determined daily as the ratio of the number of distinct body sites (dbs) colonized with identical strains over the total number of dbs tested; a mean of 5.3 dbs per patient was obtained. All isolates ($n = 322$) sequentially recovered were characterized by genotyping using contour-clamped homogeneous electrical field gel electrophoresis that allowed strain delineation among *Candida* species.

## Results
Twenty-nine patients met the criteria for inclusion; all were at high risk for *Candida* infection; 11 patients (38%) developed severe infections (8 candidemia); the remaining 18 patients were heavily colonized, but never required intravenous antifungal therapy. Among the potential risk factors for candidal infection, three discriminated the colonized from the infected patients—i.e., length of previous antibiotic therapy ($p < 0.02$), severity of illness assessed by APACHE II score ($p < 0.01$), and the intensity of *Candida spp* colonization ($p < 0.01$). By logistic regression analysis, the latter two were the independent factors that predicted subsequent candidal infection. *Candida* colonization always preceded infection with genotypically identical *Candida spp* strain. The proposed colonization indexes reached threshold values a mean of 6 days before *Candida* infection and demonstrated high positive predictive values (66 to 100%).

## Conclusions
The intensity of *Candida* colonization assessed by systematic screening helps predicting subsequent infections with identical strains in critically ill patients. Accurately identifying high-risk patients with *Candida* colonization offers opportunity for intervention strategies.

Yeasts are not inherently pathogenic for humans. Alterations of host cellular defenses, physiology, or normal flora must occur before colonization, infection, and fungal disease evolve. Candidal infections are most common in patients with neutropenia and cancer.[1-3] Recently, however, it has been recognized that the incidence of *Candida* infections is increasing in critically ill patients without the latter conditions.[4-7] National and regional statistics suggest that the rates of *Candida spp* bloodstream infections have increased markedly during the past decade.[7-11] A fivefold increase in nosocomial bloodstream infection rates has been observed in large teaching U.S. hospitals between 1980 and 1989.[12]

Although the pathogenesis of systemic candidiasis is not completely understood, the likely initial step is patient's colonization. Wey and colleagues identified *Candida* colonization as an independent risk factor for candidemia.[11] Previously, Solomkin and colleagues reported the importance of *Candida* colonization for the development of subsequent severe infections in patients recovering from abdominal surgery.[4]

Unexplained fever, signs of hypotension, and organ failure are common in critically ill patients, including patients with *Candida* overgrowth. The difficulty in treating these patients is distinguishing colonization with *Candida spp* from invasive infection.[13] Multiple surveillance cultures often are performed daily for critically ill patients, but the clinical importance of positive *Candida spp* cultures has not been defined; no current recommendation exists for initiating topical or systemic therapy based on the degree of colonization.

We conducted a prospective study in critically ill patients to question the role of yeast colonization in subsequent infection. We used genotypic typing that allows both interspecies and intraspecies delineation of *Candida spp* strains.[14] *Candida* infections occurred only in patients colonized previously with strains showing the same DNA profile. We report herein the relationship between the degree of *Candida* colonization and subsequent infection, and compare it with other risk factors for infection.

## PATIENTS AND METHODS

The University Hospital of Geneva is a 1600-bed institution, providing primary and tertiary care. Patients admitted to the surgical and neonatal intensive care units from July 1 to December 31, 1989, were eligible for the study. Approximately 650 patients were admitted to these units during the 6 month-period surveyed. For routine microbiologic surveillance, two to three samples were obtained weekly from oropharynx or trachea and stomach. When indicated clinically, additional samples from suspect areas were cultured. We conducted a 6-month prospective study, collecting all yeast isolates recovered from patients admitted to the above mentioned units.

### Definitions

Criteria for patient inclusion in the study have been described previously.[14] Briefly, only patients with significant *Candida* colonization were included. Colonization was defined as the presence of *Candida spp* in three or more samples taken from the same or different body sites on at least 2 consecutive screening days. A patient was considered infected if there was documentation of either a candidemia or a severe (see following definition) *Candida spp* infection requiring the use of systemic antifungal therapy (amphotericin B).

Candidemia was defined as 1) one blood culture that grew *Candida spp* and either histologically documented invasive candidiasis or ophthalmic examination consistent with candidal endophthalmitis; or (2) at least two blood cultures obtained at different times from a peripheral vein that grew the same *Candida spp*; or 3) one blood culture obtained peripherally and one blood culture obtained through an indwelling central line, both of which grew identical *Candida spp*. Patients with one positive blood culture drawn through an intravenous line and a positive semiquantitative catheter tip culture were not considered infected unless they satisfied one of the other criteria.

Severe nonbloodstream candidal infections were defined as *Candida spp* isolated from a normally sterile body site, and the presence of at least one of the following: fever (≥38.5 C) or hypothermia (<36 C); unexplained prolonged hypotension (systolic blood pressure <80 mm Hg > 2 hours, unresponsive to volume challenge); or absence of response to adequate antibiotic treatment for a suspected bacterial infection. *Candida spp* pneumonia required the recovery of $\geq 10^5$ cfu/mL of *Candida spp* in the bronchoalveolar lavage, in addition to the appearance of a new infiltrate on the chest-x ray. Nosocomial infections were defined according to criteria outlined by the Centers for Disease Control[15] and the Study of the Efficacy of Nosocomial Infection Control.[16]

Twenty-nine of 650 admitted patients met the criteria for inclusion and were observed prospectively for follow-up by one investigator. Decisions regarding diagnosis or antimicrobial therapy for suspected or confirmed infec-

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tions were made independently by the physicians caring for the patient.

We retrospectively reviewed all the results of the blood cultures performed at our institution during the study period and did not find any additional case of candidemia in patients admitted in the surveyed units. Four other patients in the hospital had candidemia during the study period; a chart review confirmed that these patients had never been admitted to the surveyed units and thus, were not included in the study.

## Objective and Study Variables

The primary objective of the study was to determine the role of *Candida* colonization in the development of subsequent infection. Therefore, we compared it with other risk factors for infection in critically ill patients. For this purpose, the colonization process was quantified, and patient characteristics that may have predisposed them to candidal infections were collected.[3,11,17]

A clinical examination was performed at the beginning of colonization with *Candida spp* (study entry) and every 2 to 3 days during the study period. The following characteristics were recorded: age; sex; disease severity (McCabe classification and APACHE II score[18,19]); surgical procedure(s); drug therapy (including antimicrobial agents, steroids, cytotoxic drugs, parenteral nutrition, antacids/H2-antagonists); number of indwelling medical devices in place for 3 or more days (central venous and arterial lines, bladder catheters, endotracheal tubes, surgical drains); length of hospital and intensive care unit (ICU) stay; microbiologic data; concomitant bacterial infections; and outcome. The team caring for the patients was blinded to the objectives of the study and thus to the assessment of the colonization indexes.

## Microbiology

Microbiologic methods have been described extensively elsewhere.[14,20] In brief, all 322 isolates collected during the 6 months of the study were identified by morphology and germ tube production, then characterized by phenotyping (API 1D-32C, BioMerieux, France) and genotyping—electrophoretic karyotyping—using contour-clamped homogeneous pulsed field gel electrophoresis.[14,20]

The results of semiquantitative cultures were reported as light, moderate, or heavy growth for all except gastric juice and urine specimen. Light, moderate, and heavy *Candida spp* growth in the latter samples correspond to the recovery of $\leq 10^3$, $10^4$, and $\geq 10^5$ cfu/mL, respectively.

## Candida Colonization

Once included in the study, a *Candida* colonization index (CI) was determined daily for each patient. The CI of a patient was defined as the ratio of the number of nonblood dbs colonized by *Candida spp* to the total number of body sites cultured. With the exception of blood cultures, samples collected from body sites other than those routinely screened also were considered in the CI. *Candida spp* were considered as pathogens when isolated either in pure or mixed culture. Only strains of *Candida spp* with identical electrophoretic karyotype were considered in calculating the CI. The *Candida spp* corrected colonization index (CCI) refers to a modification of the CI. The CCI takes into account both the density and the degree of colonization of *Candida spp* recovered in the semiquantitative cultures.[21] The CCI results from the product of the CI times the ratio of the number of dbs showing heavy growth to the total of dbs growing *Candida spp*. The CCI represents a *post hoc* improvement.

## Statistical Analysis

Once included, patients were observed until discharge from the hospital. Because routine microbiologic surveillance was performed concurrently only in the critical care units, the CIs were not calculated after discharge from these units. Patient's characteristics were compared by means and statistical significance assessed by the Mann-Whitney *U* test (with correction for ties when appropriate) for continuous variables, Fisher's exact test and exact test for conditional distribution[22] for categorical variables. All reported p values are two-sided. A p value $< 0.05$ was considered significant.

The model for the binary response variable (candidal infection) was built using logistic regression. The nine variables entered were age; length of ICU stay before infection in infected patients/discharge from the ICU in colonized patients; total duration of *Candida spp* colonization; duration of antibiotic therapy before colonization with *Candida spp;* total duration of antibiotic therapy; CCI; APACHE II score; number of indwelling medical devices; and number of bacterial infections documented before *Candida spp* infection. All variables that met the 0.15 significance level for entry into the model were considered by the logistic regression procedure; only those with p values less than 0.05 are reported. All statistical analyses were carried out using procedure LOGIST in the Statistical Analysis System (SAS-version 6).

# RESULTS

## Patient Characteristics

During the study period, 29 of a total of about 650 patients met the criteria for inclusion. All 29 patients were studied and observed until discharge. There were 23 male and six female patients. The majority were adults

admitted in the surgical ICU (28/29 patients, 97%). Our study population included two groups (Table 1). Eleven patients developed a severe *Candida spp* infection: eight patients had candidemia, one had septic thrombophlebitis, one had shunt ventriculitis, and one had biopsy-proven sternal osteomyelitis. Those patients will be referred throughout the text as "infected" patients. The remaining 18 patients ("colonized" patients) were heavily colonized with *Candida spp* but never developed candidal infection. Whereas all infected patients received intravenous antifungal therapy, none of the 18 colonized patients did.

Age, sex ratio, and primary diagnosis for admission were comparable in the two groups (Table 1). Most patients had severe underlying conditions according to the classification proposed by McCabe and Jackson.[18] The APACHE II score more appropriately reflected both the severity and acuity of illness and significantly differed between the two groups. The patients who ultimately developed *Candida spp* infections had higher APACHE II scores at the admission than those who did not ($p < 0.01$).

All patients were at high risk for nosocomial infections based on the models of Craven and colleagues.[23] The patients met almost all the criteria strongly predictive for infection (ICU stay >10 days, prior surgical procedure, presence of organ failure, and use of multiple invasive devices; Table 1). Consequently, the rate of bacterial infection was very high in our study population (69.4 infections per 1000 patient-days). However, bacterial infections rates were not statistically different in the two groups of patients ($p = 0.68$, Mann-Whitney).

## Potential Risk Factors for Candida Infection

The extensive use of medical devices characterized our population; all the patients had one or more central venous lines; 24 of 29 (83%) received parenteral nutrition; 22 of 29 (72%) had a bladder catheter; and more than half of the patients had an arterial line and required mechanical ventilation for more than 3 days. Ten patients required hemodialysis (34%). All patients received antacids or H2-antagonists. Although these factors can predict the development of candidemia,[3,11,17] they did not differentiate the two groups of patients in our study.

The use of broad-spectrum antibiotics, in particular when more than two drugs are used, has been shown to be associated with an increased risk for candidal infections.[3,6,10,11,17,24] In this study, 19 of 29 patients (66%) received more than two antibiotics before candidal infection ("infected" patients) or at some time during their stay within the critical care units ("colonized" patients). The duration of exposure to antibiotics in infected patients averaged 28 days at the time of candidal infection

**Table 1. CLINICAL CHARACTERISTICS OF PATIENTS WITH *CANDIDA* COLONIZATION OR INFECTION**

| | Colonized Patients (n = 18) | Infected Patients (n = 11) | p Value |
|---|---|---|---|
| Age (yrs) | 45 ± 19 | 51 ± 15 | 0.48* |
| Sex ratio (M/F) | 13/5 | 10/1 | 0.36† |
| Diagnosis | | | 0.24‡ |
| Trauma | 7 | — | |
| Surgical | 6 | 6 | 1.00† |
| Digestive | 2 | 3 | |
| Cardiovascular | 2 | 3 | |
| Other | 2 | — | |
| Medical conditions | 5 | 5 | 1.00† |
| Severity of illness | | | |
| Mc Cabe | | | 0.10‡ |
| Rapidly fatal | 5 | 3 | |
| Ultimately fatal | 8 | 4 | |
| Not fatal | 5 | 4 | |
| APACHE II | 17 ± 4 | 28 ± 6 | <0.01* |
| Length of ICU stay (days) | 17.5 (± 20) | 27.7 (± 26) | 0.12* |
| Type of antibiotic therapy§ | | | 0.47‡ |
| Single therapy | 4 | 2 | 0.62† |
| More than 2 antibiotics | 11 | 8 | 1.00† |
| Prophylaxis only | 3 | 1 | 1.00† |
| Duration of antibiotic therapy (days) | | | |
| Before colonization | 7 ± 8 | 12 ± 8 | 0.03* |
| Before infection | | 28 ± 14 | <0.02* |
| Total duration | 16 ± 13 | 35 ± 14 | <0.01* |
| Number of medical devices ‖ | 3.7 ± 1.4 | 3.6 ± 1.6 | 0.94* |
| Hemodialysis | 6 | 4 | 1.00† |
| Immunosuppressive therapy | 2 | 3 | 0.33† |
| Previous surgery¶ | 11/18 (61%) | 8/11 (72%) | 0.44† |
| Abdominal | 3 | 7 | |
| Cardiothoracic | 2 | 2 | |
| Other | 8 | 3 | |
| Concomitant nosocomial infections | | | |
| Bacteremia | 4 | 6 | |
| Pneumonia | 11 | 2 | |
| Urinary tract infection | 2 | 2 | |
| Wounds | 2 | 1 | |
| Peritonitis | 2 | 6 | |
| Others | 3 | 2 | |
| No. of bacterial infections | | | |
| Per patient | 1.38 ± 1.2 | 1.54 ± 1.3 | 0.73* |
| Per 1000 patient (days) | 76.2 | 62.4 | 0.68* |
| Site Colonization | | | |
| Mean *Candida* CI | 0.47 ± 0.17 | 0.70 ± 0.17 | <0.01* |
| Mean *Candida* CCI | 0.16 ± 0.12 | 0.56 ± 0.10 | <0.01* |
| Fatality (at 30 days) | 2 (11%) | 6 (55%) | 0.03† |

Values are mean ± S.D.
All p values are two-tailed and $p > 0.05$ are considered nonsignificant.
* Mann-Whitney *U* test (with correction for ties when appropriate).
† Fisher's exact test.
‡ Exact test for conditional distribution.[20]
§ Type of antibiotic treatment before infection in "infected patients".
‖ Medical devices (arterial and central venous lines, Foley catheter, endotracheal tube, surgical drains) left in place for >2 days were considered.
¶ Some patients had multiple surgical procedures: only the procedures affecting different anatomical systems were taken into account.
CI = colonization index, which refers to the number of distinct non-blood body sites (dbs) colonized by *Candida spp* over the total number of distinct sites tested per patient; CCI = corrected colonization index, which results from the product of the CI times the ratio of the number of dbs showing heavy growth to the total of dbs growing *Candida spp*.

**Table 2. CLINICAL VALUE OF *CANDIDA SPP* COLONIZATION PARAMETERS***

| Colonization Parameters | Sensitivity | Specificity | Positive Predictive Value† | Negative Predictive Value |
|---|---|---|---|---|
| No. of distinct body sites colonized with *Candida spp* | | | | |
| Two sites or more | 100 | 22 | 44 | 100 |
| More than two sites | 73 | 56 | 50 | 77 |
| Three sites or more | 45 | 72 | 50 | 68 |
| *Candida* colonization index | 100 | 69 | 66 | 100 |
| *Candida* corrected colonization index | 100 | 100 | 100 | 100 |

* Clinical value refers to the calculated sensitivity, specificity, positive and negative predictive values of the listed parameters (number of distinct body sites colonized with *Candida* spp and *Candida* colonization indexes) of *Candida* spp colonization to predict subsequent candidal infection. Candida colonization indexes have been calculated as described in the Methods and footnote to Table 1.

† Positive and negative predictive values have been calculated taken into account the prevalence of infection in the study population (37.9%, 11/29 patients).

and was significantly longer than the total length of exposure to antibiotics in colonized patients (16 days, $p < 0.02$). Importantly, the length of antibiotic therapy before colonization was significantly longer in the group of patients who developed infection ($p = 0.03$, Table 1).

## Candida Colonization

All 322 isolates of *Candida spp* were characterized and classified using electrophoretic karyotyping. This technique permitted discrimination between strains of the same *Candida* species.[14,20,25,26] Contour-clamped homogeneous electrical field gel electrophoresis demonstrated greater sensitivity than restriction enzyme analysis as typing system for *C. albicans*.[26] In the present study, individual patients were invariably colonized with *Candida spp* with an identical electrophoretic karyotype.[14] The recovery of isolates with similar electrophoretic karyotype pattern was patient-specific rather than site-specific.

All patients were heavily colonized with Candida spp. Colonization preceded infection by a mean of 25 days (range 6–70 days). The 18 patients who did not develop a candidal infection were colonized for a mean of 29 days (range 5–140 days). Thus, the duration of exposure to *Candida spp* colonization did not differ significantly in the two groups ($p = 0.80$, Mann-Whitney) and was long enough to have increased the risk for infection in colonized patients. However, the intensity of colonization differed between the two groups; heavier colonization was associated with subsequent infection ($p < 0.01$, Table 1).

Colonization at more than two sites has been proposed previously as a key to start earlier antifungal therapy in high-risk surgical population.[4,27] In our study, 8 of 18 patients (44%) were colonized at more than two sites and never developed severe candidal infection. Two patients acquired candidemia while colonized at two different sites only. The positive predictive value of this criterion was only 50% in our study population (Table 2). As shown in Table 2, the number of sites colonized with *Candida spp* did not adequately predict infection.

The *Candida* CI expresses the intensity of colonization and is the ratio of the number of nonblood dbs screening positive for *Candida spp* to the total number of dbs tested. The total number of dbs tested was 153 ($5.3 \pm 1$ dbs per patient, range 3 to 8 dbs) and did not significantly differ in the two groups of patients ($p = 0.39$, Mann-Whitney). The CI was calculated daily, and the highest indexes were assessed before infection (infected patients) were compared with the highest indexes recorded in colonized patients. The average CI differed significantly between colonized and infected patients (0.47 *vs.* 0.70, respectively, $p < 0.01$, Table 1); a threshold of $\geq 0.5$ properly identified the infected patients. All patients who ultimately developed infection reached the threshold value before infection, in comparison with 8 of the 18 patients who remained colonized ($p < 0.001$, Fisher's exact test). Although the sensitivity of the proposed index is optimal (Table 2), its positive predictive value (66%) is not.

Almost two thirds of the samples collected from patients who subsequently developed infection showed heavy *Candida spp* growth compared with only 27% of those collected from patients who did not. However, when the samples taken from the first colonized body sites were considered, an increased recovery of *Candida spp* in the semiquantitative cultures did not predict the development of subsequent infection among the two groups of patients (5/18 colonized *vs.* 5/11 infected patients, respectively; $p = 0.43$, Fisher's exact test). The bioburden (amount) of *Candida spp* identified in re-

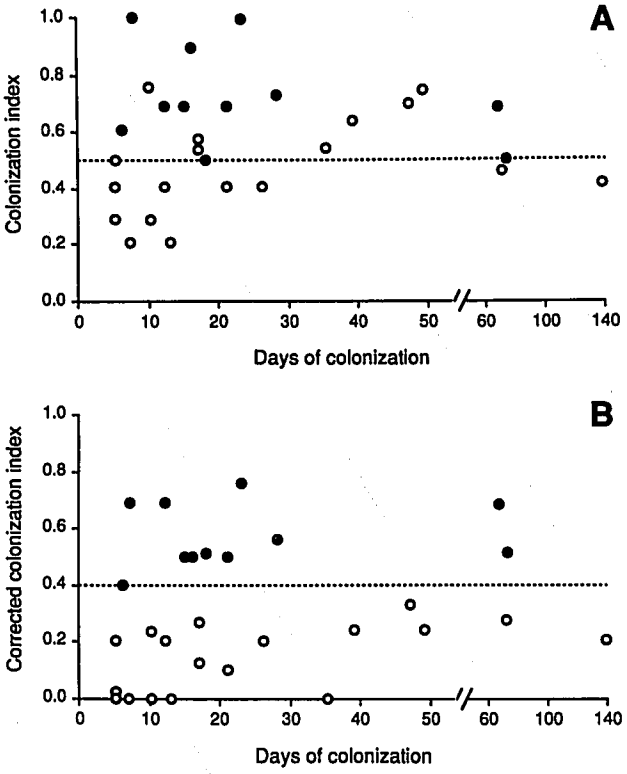


**Figure 1.** *Candida* CI in colonized and infected patients. *Candida* CI were determined daily for each patient. The CI (A) is defined as the ratio of the number of nonblood dbs colonized by *Candida spp* to the total number of body sites tested. The CCI (B) results from the product of the CI times the ratio of the number of dbs showing heavy growth to the total of dbs growing *Candida spp*. The highest CIs recorded in each patient from the first day of colonization until discharge from the unit are represented for patients who remained colonized ("colonized patients"= O) and for patients who developed candidal infection ("infected patients" = ●).

peated surveillance cultures increased with time in 3 of the 6 infected patients who did not present heavy growth initially, as well as in 3 of 13 patients in the colonized group. Taken together, either a high or an increasing count of *Candida spp* in the semiquantitative culture was close to significance in separating colonized from infected patients ($p = 0.06$, Fisher's exact test). However, two patients developed candidemia while their colonization sites only grew light to intermediate amount of yeasts.

The degree of *Candida spp* recovered by the semiquantitative cultures was used in calculating the CCI. The mean CCI significantly differed between colonized and infected patients (0.16 *vs.* 0.56, respectively; $p < 0.01$, Table 1). Whereas all colonized patients had a CCI $\leq 0.35$, all infected patients scored $\geq 0.4$. Thus, CCI separated the two groups of patients ($p \leq 0.001$, Fisher's exact test) well, and its positive predictive value was 100% in this population (Table 2).

Figure 1 reports the highest CI (Fig 1A) and CCI (Fig.1B) recorded in each patient from the first day of colonization until discharge from the unit (colonized patients) or infection (infected patients). Patients who ultimately developed infection showed higher indexes. All infected patients reached the threshold values ($CI \geq 0.5$ and $CCI \geq 0.4$, respectively) before the time of infection. Importantly, the infected patients reached the CI threshold value a mean of 6 days (range 2–21 days) before the time of infection. All but one patient reached this threshold at least 3 days before the time of infection, suggesting that earlier therapy might have been proposed in these cases. The remaining patient developed candidemia associated with a central venous line and reached the threshold only 2 days before infection.

Using multiple logistic regression procedure, the APACHE II score ($p = 0.007$) and CCI ($p < 0.001$) were the two single variables that independently predicted the development of *Candida spp* infection in the studied population. The estimated odds ratios were 1.03 ($CI_{95}$ 1.01–1.05) per point in the APACHE II score and 4.01 ($CI_{95}$ 2.16–7.45) for CCI.

## DISCUSSION

Patients admitted to intensive care units are at high risk for nosocomial infections.[7,23,28,29] In our series of 29 patients with *Candida spp* colonization or infection, bacterial infection rate was very high (69.4 infections per 1000 patient-days); 10 of 29 patients (34%) developed bacteremia and 8 (28%) developed candidemia. Studies have determined the risk factors associated with candidemia in either hospital-wide[11,17] or cancer populations.[1-3,24,30] From a hospital-wide perspective, all patients in our series presented with most of the risk factors for candidemia, such as ICU stay (100%), prior surgical procedure (90%), hemodialysis (34%), and use of multiple invasive devices (100%) and broad-spectrum antibiotics (86%). In addition, all patients were colonized with *Candida spp,* a condition that has been determined as an independent risk factor for candidemia.[11] As a consequence, a large percentage of the study patients developed severe fungal infection (11/29, 38%). When the patients who developed *Candida* infections were compared with those who did not, the only characteristics that significantly differed between the two groups were the APACHE II score at the admission ($p < 0.01$), the duration of exposure to antibiotics before colonization ($p < 0.03$) or infection ($p < 0.02$), and the intensity of *Candida* colonization ($p < 0.01$). By logistic regression, both APACHE II and the intensity of colonization proved to predict the development of *Candida* infection independently.

APACHE II score is a quantitative assessment of severity of illness and correlates with in-hospital mortality.[19,23,31] A score greater than 20 was associated with the acquisition of nosocomial infections in 43% of the pa-

tients in the study of Craven and colleagues.[23] Most of our patients (76%) scored more than 20, and patients with *Candida spp* infections scored significantly higher than those who remained colonized, both when the admission scores ($p < 0.01$, Table 1) or worst recorded scores (data not shown) were considered. (The worst APACHE II score recorded in the colonized group was compared with the worst APACHE II score before infection in the infected group.) These data suggest that the APACHE II score might be helpful to predict patients at risk for nosocomial infection, in particular to predict severe infections, such as bloodstream and fungal infections.

Others have shown that the use of broad-spectrum antibiotics increases the risk for acquiring fungal infections.[3,6,10,11,17,30] Overgrowth of *Candida spp* typically complicates these treatments, but opinions differ about its clinical significance. Previously, it was shown that the type and number of antibiotics predicted infections; our findings add to these observations because both the length of antimicrobial therapy before the beginning of *Candida spp* colonization and before infection were shown to be associated significantly with subsequent candidal infection ($p = 0.03$ and $p < 0.02$, respectively). The results reinforce the conviction that an effective restrictive antibiotic policy may be one of the most important patient care standards for preventing life-threatening infections.[32]

We previously reported the power of contour-clamped homogeneous electrical field gel electrophoresis for intraspecies delineation of *Candida spp* strains, in contrast to phenotyping techniques.[14] In particular, the former technique discriminates between strains of *C. albicans*, the most frequent colonizer in our series (24/29 patients, 83%) and the leading fungal pathogen nationwide between 1980 and 1990.[7,9,12] When patients were colonized at multiple body sites, knowledge of the electrophoretic karyotype allowed determination of the identity between strains. We believe that this approach constitutes the only possible way to address the study question, because of 1) the wide variety of strains of *Candida spp* and of *C. albicans* in particular, requiring identification below the species level,[14,25,26,33,34] and 2) the increased frequency of yeast overgrowth in critically ill patients under broad-spectrum antibiotics. All patients who developed candidal infections were colonized previously with strains with identical electrophoretic karyotypes. Using appropriate epidemiologic screening methods, the data presented prove the leading role of endogenous colonization in *Candida* infection in critically ill patients and confirm similar observation in immune-suppressed hosts.[35]

Such a role for colonization was suggested earlier by the observation of Bernardt and colleagues in 1972.[36] In 1980, Solomkin and colleagues highlighted the role of the intensity of the colonization process in the development of candidemia in surgical patients.[4] These authors also suggested that early systemic antifungal therapy may be beneficial in patients colonized who were colonized at more than two sites, but without candidemia.[27,37] Other studies on patients recovering from intra-abdominal surgery have indicated that *Candida spp* isolation in pure culture—but not in mixed culture—might constitute an indication for antifungal therapy.[5] Calandra and colleagues reported that either a high initial or increasing amount of *Candida spp* in semiquantitative cultures recovered from intra-abdominal specimens may characterize a subset of patients at higher risk for subsequent infection[21]; other body sites' colonization was not reported. In this study, we confirm this observation and extend it to sites of colonization other than the abdominal cavity. Richet and colleagues showed that high concentration of *Candida* organisms in stool constituted a significant risk factor for candidemia in patients with acute lymphocytic leukemia; the use of broad-spectrum antibiotics promoting *Candida spp* proliferation in the digestive tract was identified as an independent risk factor for infection by logistic regression analysis.[24]

The proposed CIs quantify the colonization process. In addition to systematic screening samples, we used all available specimens recovered from different body sites to mimic everyday practice in critical care settings. The indexes tend to increase with time. The number of distinct colonized sites is the best reflection of the intensity of *Candida spp* colonization, but the degree of *Candida spp* colonization at each respective site also is important. Patients who ultimately develop infection show higher indexes than those who remain colonized. Importantly, all infected patients reached the proposed threshold value before the time of infection, suggesting that earlier therapy might have been proposed in these cases. The CCI enhances the discriminatory power of the CI tested in this survey; however, the former was constructed retrospectively. Thus, the clinical value of the CCI should be tested prospectively on an independent patient population. Patients at higher risk for fungal infections, both at our institution and in several French ICUs, currently are involved in clinical trials designed for testing the potential benefit of early antifungal treatment and the value of the proposed CIs.

Our results confirm and extend data previously obtained in different patient populations. The generalizability of our findings needs to be addressed in larger studies. The high mortality of candidal infection justifies appropriately designed, controlled trials comparing early antifungal therapy in high-risk patients with significant *Candida spp* colonization. Our results also strongly reemphasize the critical importance of discontinuing antibiotic treatment as early as possible in critically ill patients.

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