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Nosocomial *Candida glabrata* Colonization: an Epidemiologic Study

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***Candida glabrata* has emerged as an important nosocomial pathogen, yet little is known about its epidemiology. We prospectively followed 98 patients admitted to a medical intensive care unit and the bone marrow transplant unit of a university hospital. Samples from environmental surfaces and the hands of hospital personnel were also cultured. Patients with newly acquired *C. glabrata* strains were compared to controls who were culture negative for *C. glabrata*. *C. glabrata* was recovered from multiple sites from 24 patients and three environmental surfaces. Sixteen patients (17%) acquired *C. glabrata* after admission to the study units. Significant risk factors for the nosocomial acquisition of *C. glabrata* were prolonged duration of hospitalization in the unit and prior antimicrobial use. Strain delineation by restriction enzyme analysis revealed 28 different strains of *C. glabrata*; three strain types were common to nine patients. The environmental isolates were of the same strain type and common to five patients (four patients with newly acquired strains). These results suggest the possibility of exogenous nosocomial acquisition of *C. glabrata*, including the possible acquisition from the hospital environment. Transmission may be by indirect contact since identical strains of *C. glabrata* were recovered from patients who were geographically and temporally associated.**

Candida species are ubiquitous organisms (26). An increasing incidence of nosocomial infections caused by *Candida* species has been noted in neutropenic patients as well as in other immunocompromised patients such as patients in intensive care and postsurgical patients (5, 6, 13, 20, 38, 39). The changing patterns and the increasing incidence of disseminated *Candida* infection have also been evident in large autopsy series (5). The high mortality rate associated with bacterial infections has declined with the early empiric administration of antibiotics, while fungal infections have increasingly become important in causing morbidity and mortality in immunocompromised patients. *Candida* is now the fourth most common organism recovered from cultures of blood from hospitalized patients (3, 4). Although *Candida albicans* is the most common fungal species isolated from blood, *Candida glabrata* ranks fourth among the *Candida* species isolated from blood (and ranks third among patients who have undergone surgery). The mortality rate from *C. glabrata* infection is as high as that from *C. albicans* infections (2–4, 20, 21). *C. glabrata* is of special importance not only because of a recent increase in its frequency but also because of its innately reduced susceptibility to antifungal agents, specifically, the azoles (10, 12, 20, 36, 41).

A clear understanding of the epidemiology of *Candida* infection and colonization has been difficult because of a lack of a reliable typing system for the evaluation of strain relatedness. Previous typing systems have relied on phenotypic differences within a *Candida* species which may not reflect true strain differences (8, 24, 37). Recent advances in the use of molecular biology-based techniques have enabled investigators to develop typing systems with greater sensitivities. These techniques have been widely used to study diverse groups of organisms including bacteria, viruses, and fungi (1, 8, 9, 15, 22, 24, 31, 34). Molecular typing of *Candida* by DNA fingerprinting has the capability of differentiating closely related strains which may have phenotypic similarities (8, 9, 18, 34).

In this prospective study, we used restriction fragment length polymorphism (RFLP) analysis, a form of molecular typing, to delineate the different strains of *C. glabrata*. This will further clarify the patient and hospital reservoirs of infection and the modes of *Candida* transmission between high-risk patients. A knowledge of the epidemiology of nosocomial colonization and infection is essential for the prevention of the further spread of *C. glabrata* and nosocomial infection.

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MATERIALS AND METHODS

Harper Hospital is a 900-bed tertiary-care teaching hospital in Detroit, Mich. Patients admitted to one medical intensive care unit (MICU) and bone marrow transplant unit (BMTU) were studied. The MICU is an eight-bed private-room unit. Patients hospitalized in the MICU were transferred midway during the study period to a separate 10-bed unit with four open beds and six private beds located on a different floor. The same hospital personnel continued to care for patients in each MICU. The BMTU is a 24-bed private-room unit with a hospital staff separate from that for the MICU. Patients were occasionally transferred between the BMTU and the MICU, depending on the severity of illness. House staff and medical students rotate between Harper Hospital and four other Wayne State University hospitals.

We prospectively studied all patients who provided informed consent and were hospitalized in the BMTU or the MICU during a 10-month study period. Demographic and clinical data, including date of hospitalization, date of discharge, age, gender, ward, and medical service were recorded. The presence of urinary catheterization and indwelling vascular catheter placement (with dates and sites) was also recorded. A careful record of bed assignments was kept, as were the patients' movements within the hospital before discharge. Exposure to antibiotics and antifungal agents (duration, route, type, and indication) and cytotoxic and immunosuppressive agents was also evaluated.

We defined colonization and infection according to established criteria. Colonization was indicated when *Candida* species were isolated from a site in the absence of signs or symptoms of infection; infection was diagnosed when the organism was isolated from a normally sterile body site, concurrent with accompanying signs and symptoms of infection. Death was considered related to *C. glabrata* if the patient died within 72 h after obtaining a culture-positive sample

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TABLE 1. Demographic and risk factor characteristics of patients and controls for the acquisition of *C. glabrata*

Characteristic	Patients with newly acquired *C. glabrata* ($n = 16$)	All patients infected or colonized with *C. glabrata* ($n = 24$)	Patients not infected or colonized with *Candida* species ($n = 33$)
Mean age (yr [range])	45.9 (19–88)	47.0 (19–88)	49.1 (5–85)
Sex (no. of males/no. of females)	3/13	4/20	20/11
Mean duration in unit (days)	18.8	17.6	7.6[a]
Mean duration in study (days [range])	35.6 (7–89)	33.0 (7–89)	39.1 (4–101)
No. (%) of patients with prior antibiotic therapy	16 (100)	16 (67)	20 (65)[a]
No. (%) of patients with prior antifungal therapy	8 (50)	8 (33)	16 (52)
No. of patients receiving prior systemic antifungal therapy	7 (3 flz)[b]	7 (3 flz)	7 (2 flz)
No. (%) of patients receiving immunosuppressive therapy	10 (63)	15 (63)	23 (74)
No. (%) of patients with granulocytopenia	9 (56)	13 (54)	14 (45)
No. (%) of patients with the following underlying illness:			
Malignancy	11 (67)	16 (66)	21 (68)
Cardiac disease	2 (13)	2 (8)	6 (19)
Neurologic disease	1 (6)	1 (4)	5 (16)

[a] $P < 0.001$; significant in multivariate analysis.
[b] Values in parentheses are numbers of patients receiving fluconazole (flz).

from a normally sterile body site, the clinical profile was consistent with systemic infection, and no other evident reason for death was ascertained. The scale of McCabe and Jackson (23), in which class 1 is a nonfatal underlying disease, class 2 is an ultimately fatal disease (50% chance of death within 5 years), and class 3 is a rapidly fatal disease (50% chance of death within 2 months), was used to categorize the severity of illness.

Specimens were obtained from all patients. All specimens were plated on Sabouraud dextrose agar (Difco, Detroit, Mich.); clinical specimens were also plated on blood agar. Samples were obtained for culture when the patients were admitted to the study unit and then weekly for patients in the BMTU and biweekly for patients in the MICU until discharge from the unit. Oropharyngeal, rectal, and urine samples from all patients were cultured. Specimens from other sites such as wounds, vagina, skin, and blood were also taken when it was clinically indicated. The dates that samples were obtained, the sampling sites, and colony counts of cultures positive for yeast were recorded. Oropharyngeal and rectal specimens were obtained with a sterile cotton swab. Urine samples were obtained through clean-catch voiding or were taken from syringe-aspirated catheters. Fifty hand samples from 25 hospital personnel in both units obtained by producing an impression with the hands on a petri dish with Sabouraud dextrose agar (Difco) were cultured (27, 30, 42). Fifty samples from selected environmental surfaces and 10 samples of patient food from the study units were cultured by using Rodac plates with Sabouraud dextrose agar (Falcon, Oxnard, Calif.). Environmental samples from the surfaces, food, and hands were cultured at the beginning of the study and at 3-month intervals. Surfaces in a second MICU (MICU-II) were also assessed by culture when the location of the unit was changed during the study period and before any patients were hospitalized in the new unit.

All patients with positive *C. glabrata* cultures were compared to control patients from whom no yeast species were recovered at any time during the study period. All patients hospitalized in the MICU and the BMTU during the study period were evaluated. Dichotomous variables were compared by using the chi-square test or two-tailed Fisher's exact test. Continuous variables were compared by the Mann-Whitney U test. A multivariate logistic regression model was used to evaluate independent risk factors for *C. glabrata* colonization (14, 19).

Candida species were identified by germ tube and chlamydospore formation, morphology, and the Yeast API 20C method (Sherwood Medical, Plainview, N.Y.). Strains were initially isolated on Sabouraud dextrose agar (Difco) and were stored frozen at −70°C until analysis. Control strains of *C. glabrata* were strains obtained from 10 patients located in geographically separate hospitals and *C. glabrata* ATCC 2001 (American Type Culture Collection, Rockville, Md.).

Isolates were evaluated for molecular relatedness by restriction enzyme analysis (REA) of genomic DNA. The method used to prepare and analyze the DNA for comparison of the molecular relatedness of strains has been published and described previously in detail (33, 34). For electrophoresis, DNA was digested with the restriction endonuclease *Eco*RI or *Msp*I (BRL, Gaithersburg, Md.) by following the recommendations of the manufacturer. The DNA was then run on a 0.7% agarose gel at 30 V for 16 h. The gel was stained in a solution of 0.5 μg of ethidium bromide per ml and was destained in water before being photographed.

Differentiation of isolates by REA was achieved by visual comparison of the more variable bands. As has been published previously (33, 34), strains were considered different if there were two or more bands differences between isolates. The variations in these patterns formed the basis for our groups. All isolates were initially digested with *Msp*I and typed. Afterward, those isolates that were similar by *Msp*I digestion were then submitted to separate *Eco*RI digestion and were further delineated into groups.

RESULTS

During the study period, we followed 98 patients (51 men and 47 women) with 106 admissions hospitalized in the BMTU or the MICU. Six patients had two admissions each, and one patient had three admissions. Patients with positive *C. glabrata* cultures ranged in age from 19 to 88 years (mean age, 47.0 years). Patients in the MICU were hospitalized for a mean of 21 days (range, 7 to 57 days) and in the BMTU for a mean of 32 days (range, 10 to 65 days) (Table 1). Twenty-four patients (24.5%) were culture positive for *C. glabrata* at some point during their hospital stay. Of the 24 patients, only *C. glabrata* was isolated from 7 patients, whereas both *C. glabrata* and other *Candida* species were isolated simultaneously or consecutively from 17 of the patients during their hospital stay. The combination of *C. glabrata* and *C. albicans* was the most common for 11 (65%) of the 17 patients; the remaining 6 patients were colonized with *C. glabrata* and either *C. parapsilosis*, *C. kefyr*, *C. tropicalis*, or *C. lusitaniae*. For four of the remaining six patients three different *Candida* species were isolated during their hospital stay. *Candida* species other than *C. albicans* were isolated from 15 patients. Thus, 65 of the 98 study patients were colonized with *Candida* species, with an overall colonization ratio of 1:2.3 for non-*C. albicans* to *C. albicans.*

Demographic and risk factors for patients and controls are summarized in Table 1. There were no differences between patients colonized with *C. glabrata* and controls with regard to fluconazole administration. Of the 24 patients colonized with *C. glabrata*, 16 (66%) had an underlying hematological malignancy. Regarding the 16 patients with a newly acquired *C. glabrata* colonization, 11 had either leukemia ($n = 9$) or lymphoma ($n = 2$). There were no significant differences in the demographic data between patients and controls in BMTU or MICU admissions.

A total of 736 samples were cultured during the study. Six-hundred twenty-six were from patients, 60 were from the environment, and 50 were from hospital personnel. A total of 425 samples from all sources were culture positive. Of 626 samples from patients, 400 (68%) were positive for yeast during the study period. There were a mean of 6.4 samples per patient in the yeast-positive group and a mean of 4.0 samples per patient in the yeast-negative group. The majority of the positive cultures grew *C. albicans* (226 isolates; 56.6%), followed by *C. glabrata* (102 isolates; 26%), *C. lusitaniae* (32 isolates; 8%),

TABLE 2. Distribution of *C. glabrata* isolates by site of isolation and as a percentage of all *Candida* species in the study

Body site	No. of *C. glabrata* isolates	Total no. of *Candida* isolates	% of total
Oropharynx	17	128	13
Stool or rectum	44	142	31
Urine	32	72	44
Vagina	7	39	18
Blood	0	4	0
Wound	2	13	18
Sputum	0	2	0
Total	102	400	25.5

C. tropicalis (18 isolates; 4.5%), *C. kefyr* (9 isolates; 2.2%), and *C. parapsilosis* (8 isolates; 2%).

We recovered a total of 102 *C. glabrata* isolates from 24 patients, this accounted for 26% of all *Candida* species recovered. The distribution of *C. glabrata* by site of isolation is presented in Table 2. Sixteen of the 24 patients culture positive for *C. glabrata* had negative initial cultures and *C. glabrata* was isolated only after admission to the study unit. Of these, eight were in the BMTU, five were in the first MICU (MICU-I), and three were in MICU-II. Thirteen of the 24 patients colonized with *C. glabrata* were located in the BMTU, 6 were in MICU-I, and 5 were in MICU-II (Table 3). No positive hand samples from hospital staff or samples of the food given to patients were positive for *C. glabrata* by culture.

C. glabrata was recovered from 3 of the 50 environmental surface samples that were cultured. Two isolates were recovered simultaneously from different surfaces in the same room in MICU-I and one isolate was recovered in the BMTU. The colonized environmental surfaces were those that were frequently touched by hospital personnel or that were in open contact with patients: a monitor panel and a bedside tray in the same room in MICU-I and the bed rail of one patient room in the BMTU. No common source (vehicle) was identified. The most commonly recovered organisms from the environmental surfaces evaluated were *C. albicans* (eight isolates), *C. lusitaniae* and *C. parapsilosis* (2 isolates each), and *C. guilliermondii* (one isolate). Additionally, 32% of the 25 personnel whose hand samples were cultured carried *C. parapsilosis* on their hands.

REA was performed with 115 isolates of *C. glabrata*: 102 isolates recovered from 24 study patients, 3 isolates recovered from environmental surfaces, and the 10 control strains. REA revealed 28 different patterns (strain types) among the isolates. Figure 1 demonstrates the RFLP patterns for the most frequently encountered strain types (types 01, 04, 05, and 12), comprising 41% of all *C. glabrata* isolates. These four types were common to 10 patients and the three environmental isolates. Strains of types 01 and 02 were similar except that the double bands found between the 9.4- and 22-kb range were different for both the two types. It is as noteworthy, that, published previously (34), most of the differences among the *C. glabrata* isolates are generally detected in the higher-molecular-size ranges of 9.4 to 23.1 kb.

Overall, group 01 consisted of eight isolates from five different patients and 3 environmental samples, group 04 consisted of nine isolates from two patients, group 05 consisted of seven isolates from a single patient at various times, and group 12 consisted of five isolates from two patients. The isolates from the remaining patients and controls were distinctly different strain types with unique RFLP patterns.

Patients with newly acquired *C. glabrata* strains and strains with identical types were temporally and geographically associated in BMTU rooms 3, 12, 13, and 20 for strain type 01 and in rooms 19 and 22 for strain type 07 (Fig. 2). Additionally, patients in rooms 4, 5, 7, 10, and 13 were also colonized with newly acquired strains of *C. glabrata*. Patients in MICU-I colonized with newly acquired strains were found in rooms 26, 27, 28, and 31 (Table 3; Fig. 2). We found no environmental isolates or shared strains in MICU-II, although one patient transferred from MICU-I was colonized in MICU-II with a strain that was of the same type as the environmental isolates in MICU-I. In addition, patients in rooms 27, 31, and 33 in MICU-II were also colonized with newly acquired strains of *C. glabrata*. Evaluation of isolates colonizing different body sites of an individual patient revealed that 14 (58%) of 24 patients were colonized with the same strain type at multiple anatomical sites. For five patients two different strains of *C. glabrata* were recovered from different sites or at different times, and for two patients three different strain types were isolated. For 17 (70%) of the 24 patients, *C. glabrata* was isolated with at least another *Candida* species. Prospective longitudinal cultures of samples from 12 patients showed carriage of the same strain in 8 patients (75%).

There was only one clinical infection with *C. glabrata*, and this occurred in a diabetic patient with fungal pyelonephritis and urinary obstruction. Nine of the 24 patients whose samples were culture positive for *C. glabrata* died. However, no deaths were directly attributed to *C. glabrata*.

It is also of interest that among the 24 patients infected or colonized with *C. glabrata*, 13 also had episodes of bacteremia. The most commonly isolated organisms included *Staphylococcus epidermidis* ($n = 4$), enterococcus ($n = 2$), *Streptococcus pneumoniae* ($n = 1$), group C *Streptococcus* ($n = 1$), and viridans group streptococcus ($n = 1$). Additionally, seven patients had bacteremia caused by gram-negative organisms. The association between *C. glabrata* colonization and bacteremia has not been observed in previously published reports describ-

TABLE 3. Patient and environmental distribution of *C. glabrata* isolates, strain types, and room numbers[a]

Unit	Total no. of patients in study	No. of patients positive for *C. glabrata*	Patients with newly acquired strains			Environmental isolates			No. of patients colonized with *C. glabrata* upon transfer to study unit
			No. of patients	Room no.	Strain type[b]	No. of isolates	Room no.	Strain type	
MICU-I	21	6	5	26, 27, 28, 31	10, 15, 18, 23, 24	2	26	01	1
MICU-II	23	5	3	27, 31, 33	01, 02, 19, 25	0			2
BMTU	54	13	8	3, 4, 5, 7, 10, 12, 13, 19, 20, 22	01, 02, 06, 07, 08, 09, 20	1	3	01	5

[a] Refer to Fig. 2 for descriptions of the different strain types.
[b] One strain was common to five patients and three environmental surfaces.

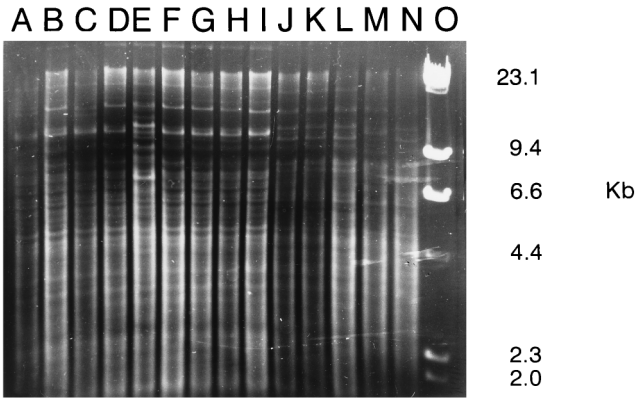

FIG. 1. Agarose gel electrophoresis of chromosomal DNA of *C. glabrata* with the restriction enzyme *Msp*I. Lane O, bacteriophage lambda digested with *Eco*RI, used as a control; lanes A to G and J to N, clinical isolates from 12 separate patients; lanes H and I, environmental isolates; lane A, strain type 12; lanes B, D, F, G, H, and I, strain type 02; lane C, strain type 01; lane E, strain type 03; lanes J, K, L, and N, strain type 04; lane M, strain type 05.

ing the nosocomial epidemiology of several of the *Candida* species from this same population of patients (29, 30, 35).

DISCUSSION

Candida species are important opportunistic pathogens causing nosocomial infections because of their ability to infect seriously ill hospitalized patients (5, 11, 20, 25, 28, 38). In the past, *C. albicans* accounted for approximately 80 percent of all isolated fungi causing nosocomial infections (3, 4). Most published studies on nosocomial *Candida* acquisition have evaluated *C. albicans*, but few studies have evaluated the *Candida* species other than *C. albicans.*

Most reports describing the epidemiology of nosocomial *C. glabrata* infections have been retrospective and have identified risk factors for *Candida* infections, but few studies have evaluated independent risk factors associated with nosocomial *C. glabrata* acquisition. In the present study, a multivariate prospective case-control analysis and a molecular biology-based analysis of *C. glabrata* demonstrated that patients with newly acquired *C. glabrata* colonization or infection had longer durations of hospitalization and more frequent prior antimicrobial use compared with those for patients from whom *Candida* species were not recovered. There were no differences between patients from whom *C. glabrata* was isolated and controls. These results are similar to the findings noted in earlier epidemiological studies of *C. albicans*, *C. lusitaniae*, and *C. parapsilosis* (13, 20, 29, 30, 35).

Little is known about the hospital reservoirs of *C. glabrata*, but as with *C. albicans*, probable sources include a complex interaction of environmental and human reservoirs (16, 35). The unique role of the environment as a potential reservoir for *Candida* species is further suggested by findings in the present study in which identical strains of *C. glabrata* were isolated from the environment prior to the new acquisition of *C. glabrata* by patients in the BMTU, thereby suggesting the potential acquisition of the organism from the hospital environment. The significance of this observation is that fungal organisms isolated from the inanimate hospital environment were previously considered to contribute negligibly to nosocomial fungal infections. Although infecting strains can be cultured from environmental surfaces, it is believed that the environment becomes passively contaminated with organisms from patients, as was demonstrated in our prior study (35) and again in this study. The results of this study suggest that *C. glabrata* may be similar to *C. albicans* and not unlike other nosocomial pathogens that can potentially be acquired directly or indirectly from contaminated environmental surfaces.

Previous understanding of the pathogenesis of *C. glabrata* acquisition, colonization, and infection indicates that the organisms are endogenously acquired exclusively from the patient's own flora. What has not been previously studied is the mechanism by which and the extent to which hospitalization contributes to colonization with *C. glabrata*. Two studies have implicated carriage on the hands of hospital personnel as a possible source of outbreaks (17, 35).

Many of these previous epidemiological reports have been hampered by the lack of an adequate typing system for the delineation of the *Candida* species. In our prior studies (33–35) we have used a contour-clamped homogeneous electric field as our optimal strain delineation system. However, we have previously demonstrated that for *C. glabrata*, REA (RFLP analysis) had a greater sensitivity in detecting subtle strain-to-strain variations; thus, this methodology was chosen to investigate our isolates in this study (34). For the most part, lack of strain typing and the lack of prospective surveillance cultures have made it difficult to delineate the epidemiology of *C. glabrata* colonization and infection.

Initially, 67% of the patients were culture negative for *C. glabrata* and possibly acquired the organism while in the study unit. The isolation of identical strains of *C. glabrata* from patients who were geographically and temporally associated suggests that a route of transmission may be indirect contact between patients. The epidemiology of the nosocomial acquisition of *C. glabrata* may therefore be similar to the epidemiology of *C. albicans*, methicillin-resistant staphylococci, multidrug-resistant enterococci, and gram-negative bacilli (35, 42).

One important mechanism for nosocomial infection seems to be the transient carriage from colonized or infected patients on the hands of personnel (35, 42). The role of carriage by personnel in the dissemination not only of *C. glabrata* but also of other *Candida* species remains to be clarified. Although *C. glabrata* was not recovered from the hands of hospital per-

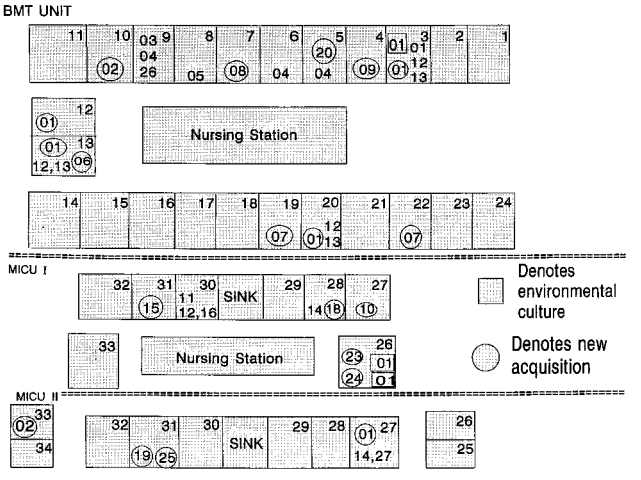

FIG. 2. Schematic floor plan of the MICU and the BMTU. Circled numbers denote patients with newly acquired *C. glabrata* isolates. Squared numbers denote environmental samples culture positive for *C. glabrata*. The numbers 01 to 27 denote the separate strain types isolated from patients and the environment. The numbers 1 to 24 and 25 to 34 in the upper right-hand corner of each box denote patient room numbers.

sonnel in this study, transient carriage is suggested by the isolation of *C. glabrata* on environmental surfaces in contact with hands. Perhaps more frequent culturing of samples from the hands of hospital personnel or the use of liquid medium for the recovery of yeast may have improved the rates of detection of *C. glabrata*. In addition, our culture methods for the detection of yeast may have missed low numbers of yeast in some patients. *C. glabrata* seemed to be transmitted between patients in adjacent beds within the study units. Proximity to a patient with infection or colonization increased the risk of acquisition. As in earlier studies (28, 32, 35), results of longitudinal cultures showed that over time patients (75%) in the present study generally carried a *C. glabrata* strain of the same type. There was minimal diversity among strains from individual patients. This finding is in contrast to the results described for the nosocomial acquisition of *C. albicans*, in which there was considerable strain diversity (35). Moreover, in this study, more than one *Candida* species was isolated from 71% of patients with culture positive for *C. glabrata*. The most frequent combination was *C. glabrata* and *C. albicans* for approximately 70% of the patients. This again is in contrast to the findings previously described for *C. albicans* since more than one *Candida* species was identified in only 39% of patients infected or colonized with *C. albicans* (38).

In contrast to the epidemiology of *C. albicans*, no *C. glabrata* isolates were identified in the food given to the hospitalized patients. Another interesting finding in this study is the high degree of bacteremia (54%) in patients with *C. glabrata* colonization. Although the microbiology of bacteremia was diverse, most of the pathogens isolated are those generally found in the gastrointestinal tract or skin of hospitalized patients.

In conclusion, the findings of this prospective study suggest that the nosocomial acquisition of *C. glabrata* is not uncommon and may be due to the exogenous acquisition of the *Candida* species. In addition, we have been able to demonstrate that two-thirds of the patients demonstrated *C. glabrata* colonization after hospitalization and that the two major risk factors were prolonged duration of hospitalization and prior antimicrobial use. Additionally, we have also shown that when *C. glabrata* was isolated from patients, it was frequently accompanied by a second *Candida* species (usually *C. albicans*) and it was infrequently the only species of yeast colonizing the patients. Further prospective studies are needed to define more clearly the reservoirs of infection as well as the mode of transfer and the measures for preventing spread.

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