Epidemiologic and Molecular Characterization of an Outbreak of *Candida parapsilosis* Bloodstream Infections in a Community Hospital

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Candida parapsilosis **is an important cause of bloodstream infections in the health care setting. We investigated a large *C. parapsilosis* outbreak occurring in a community hospital and conducted a case-control study to determine the risk factors for infection. We identified 22 cases of bloodstream infection with *C. parapsilosis*: 15 confirmed and 7 possible. The factors associated with an increased risk of infection included hospitalization in the intensive care unit (adjusted odds ratio, 16.4; 95% confidence interval, 1.8 to 148.1) and receipt of total parenteral nutrition (adjusted odds ratio, 9.2; 95% confidence interval, 0.9 to 98.1). Samples for surveillance cultures were obtained from health care worker hands, central venous catheter insertion sites, and medical devices. Twenty-six percent of the health care workers surveyed demonstrated hand colonization with *C. parapsilosis*, and one hand isolate was highly related to all case-patient isolates by tests with the DNA probe Cp3-13. Outbreak strain isolates also demonstrated reduced susceptibilities to fluconazole and voriconazole. This largest known reported outbreak of *C. parapsilosis* bloodstream infections in adults resulted from an interplay of host, environment, and pathogen factors. Recommendations for control measures focused on improving hand hygiene compliance.**

In the United States, the incidence of bloodstream infections (BSIs) with *Candida* species is 6 to 14 per 100,000 persons per year (4, 11). The rate of mortality associated with *Candida* BSIs can approach 50% (10). Almost 80% of these infections, including those in the intensive care unit (ICU) (36%) and outpatient (25%) settings, occur in persons in whom a central venous catheter (CVC) has been placed (11). *Candida parapsilosis* is widely recognized as a cause of BSIs among hospitalized patients, particularly in neonates, and the association of *C. parapsilosis* fungemia with CVCs and parenteral nutrition is well appreciated (5, 11, 19, 26, 27). Outbreaks and clusters of cross-transmission, both in ICU patients and in outpatients, have been attributed to extrinsic contamination of CVCs, total parenteral nutrition (TPN) solutions, intravascular devices, and medications (3, 4, 13, 16, 22–25, 28).

In April 2001, infection control practitioners at a large community hospital (hospital A) noted an increase in the frequency of isolation of *C. parapsilosis* strains from cultures of blood and CVC tips from adult inpatients. We describe the results of the epidemiologic and laboratory investigations of this outbreak of *C. parapsilosis* BSIs.

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MATERIALS AND METHODS

Definitions and ascertainment of cases. To describe the extent of the outbreak and define a study period, we examined the annual catheter-associated BSI rates in the medical, surgical, and neurological ICUs of hospital A for 1999, 2000, and the first 6 months of 2001 using existing data from active surveillance for catheter-related BSIs. Hospital A used standard National Nosocomial Infection Surveillance System methods and case definitions for surveillance purposes (12).

We defined a confirmed case patient as a patient for whom *C. parapsilosis* was isolated from a blood culture at least 48 h after admission to hospital A during the outbreak period, defined as April 2001 (the first detectable increase in infection) through October 2001 (the date of the on-site investigation). We defined a possible case patient as a patient for whom *C. parapsilosis* was isolated from a CVC tip culture at least 48 h after admission to hospital A during the outbreak period, in the absence of a bloodstream isolate. Possible cases were believed to represent CVC colonization or, in some cases, a possible BSI (e.g., a CVC was removed because of a presumed BSI, but a culture of blood was sterile). Cases were identified by reviewing clinical microbiology laboratory records for all patients from whom *Candida* species was isolated in culture from any patient source during the study period.

Epidemiologic studies. We conducted a case-control study to determine the potential risk factors for *C. parapsilosis* BSIs. Confirmed and possible cases were included in the study and the initial analysis. Two control patients were included for each case patient and were randomly selected from all inpatients of hospital A during the outbreak period. The case and the control patients were frequency matched by age group (18 to 44, 45 to 70, or >70 years) and the length of hospitalization prior to a positive culture for the case patient. Potential control patients were excluded if they had been hospitalized for less than 7 days, the minimum total length of stay for case patients.

Demographic and clinical data were abstracted from medical records by using a standardized form. Data collected included prior BSIs; procedures; and the use of CVCs, medications, and infusions. Data regarding the durations of exposure

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were recorded from the date of admission until the index day (the hospital day on which the first sample positive for *C. parapsilosis* by culture was collected) for case patients and the corresponding day for the matched controls.

Procedural investigation. We examined patient care areas and other areas in the three ICUs and reviewed infection control and isolation policies and practices. We also conducted three surreptitious observational studies of health care worker (HCW) hand hygiene practices. These observations were 60 min each and were performed during separate nursing shifts. During the observational studies, we noted whether contact with patients occurred and whether hand hygiene was performed before and after each contact. In addition, we observed practices associated with TPN and lipid administration and the placement and care of CVCs.

Laboratory studies. Eighteen patient isolates were sent to the Fungus Reference Unit, Centers for Disease Control and Prevention (CDC), for confirmation of the identification. These included five blood and two CVC tip isolates obtained from case patients during the outbreak period, three isolates obtained during the outbreak period from case-patient body sites other than blood or CVC tips, two isolates obtained during the outbreak period from patients in hospital A who did not meet the case definitions, and six blood or CVC tip isolates obtained from patients subsequent to the outbreak period. Isolates were identified at CDC by using ChromAgar *Candida* (DRG International, Mountainside, N.J.), the API 20C system (bioMerieux, St. Louis, Mo.), and cornmeal Dalmau plates.

Culture surveys and microbiologic methods. To investigate the role of cross-transmission of *C. parapsilosis* in this outbreak, we determined the prevalence of *Candida* hand colonization in a sample of HCWs in the three ICUs by culturing samples from the hands by the handiwipe method (18). The HCWs surveyed included day- and night-shift nurses, physicians, phlebotomists, respiratory therapists, radiology technicians, and dialysis technicians. We surveyed HCWs regardless of the length of time on duty, the timing of hand hygiene, or their specific patient care activities.

To determine the prevalence of skin colonization with *C. parapsilosis* among ICU patients, a cross-sectional survey of medical-surgical and neurological ICU patients was done on 5 November 2001. Swabs for fungal culture were obtained from the CVC insertion sites and CVC hubs from all patients. We also cultured electrocardiograph leads and the blood pressure cuff tubes in each patient room in the medical-surgical ICU.

All environmental samples were sent to CDC for processing. Each handiwipe was returned in a sterile container. After the addition of 50 ml of sterile 0.02% Tween 80 in water, the container was agitated on a shaker for 30 min; the liquid was then drained into a 50-ml tube and centrifuged at $3,000 \times g$ for 10 min. The pellet was resuspended in 200 μl of fresh Tween solution, and aliquots were plated on ChromAgar *Candida* (DRG International) and Sabouraud dextrose agar with chloramphenicol. The species of all yeast isolates were determined by using the API 20C system (bioMerieux) and cornmeal Dalmau plates.

Molecular typing of all *C. parapsilosis* isolates was performed by randomly amplified polymorphic DNA (RAPD) analysis, electrophoretic karyotyping, and Southern blotting with the complex Cp3-13 probe (6) by a nonisotopic development method. The Southern blot was analyzed with BioNumerics software (Applied Maths, Austin, Tex.) by using the unweighted pair-group method with arithmetic averages algorithm for cluster analysis (1, 6). Broth microdilution testing for susceptibilities to fluconazole, itraconazole, and voriconazole was performed by standard NCCLS methods (17).

Statistical analysis. Univariate analysis was performed with SAS software (version 8.2, 1989-2000; SAS Institute, Cary, N.C.). Continuous data were compared by *t* tests, and categorical variables were compared by chi-square tests (α = 0.05). The Wilcoxon rank sum test was used for data that were not normally distributed. Odds ratios (ORs) were adjusted for age group and the duration of hospitalization prior to the index day by using the SAS logistic regression procedure to analyze the data for matched cases and controls. Variables were included in multivariable modeling when *P* was <0.1 by univariate analysis, and the results of multivariable modeling were considered significant when *P* was <0.1.

RESULTS

Outbreak confirmation. The CVC-associated *Candida* BSI rate in the three adult ICUs of hospital A increased fivefold in the first 6 months of 2001 compared to the rates in 1999 and 2000, from 1.0 per 1,000 CVC-days in 1999 and 2000 to 5.3 per 1,000 CVC-days in the first 6 months of 2001. This increase was
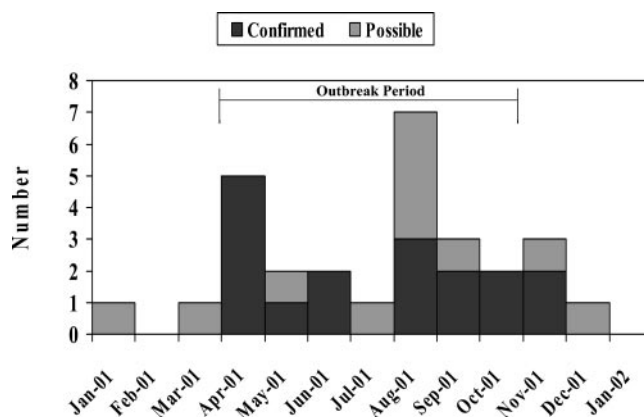

FIG. 1. Distribution of confirmed and probable *C. parapsilosis* infections by month of isolation, hospital A, Mississippi, 2001.

attributable to an almost sevenfold increase in the rate of *C. parapsilosis* BSIs, from 0 per 1,000 CVC-days in 1999 and 0.7 per 1,000 CVC-days in 2000 to 4.5 per 1,000 CVC-days in the first 6 months of 2001. During the same 6-month period in 2001, the rate of CVC-associated bacterial BSIs (3.8 per 1,000 CVC-days) remained unchanged from that in the previous year (3.6 per 1,000 CVC-days in 2000).

Descriptive characteristics. Figure 1 demonstrates the distributions of confirmed and possible *C. parapsilosis* cases by month of fungal isolation and includes incident isolates occurring before and after the outbreak period. We identified 15 confirmed cases and 7 possible cases. Of these 22 case patients, the median age was 55.5 years (range, 29 to 81 years), 12 (55%) were white, and 12 (55%) were male. All case patients had CVCs in place, and 18 (82%) had been in an ICU prior to the isolation of *C. parapsilosis*. The median time from CVC placement to the recovery of a *C. parapsilosis* isolate was 12 days (range, 3 to 29 days), and the median time from admission to isolate recovery was 20 days (range, 5 to 50 days). The median total length of hospital stay was 38 days. Nine (41%) case patients died, and six died within 7 days of recovery of an isolate.

Assessment of risk factors. Because complete medical records were unavailable for 2 of the 15 patients with confirmed cases, the case-control study included 20 case patients (13 with confirmed cases and 7 with possible cases) and 40 control patients. Case and control patients did not differ on matching characteristics; overall demographic and clinical characteristics were similar between the case and the control patients.

On univariate analysis case patients had significantly higher mean APACHE II scores than the control patients on the index day (19 and 13.7, respectively; *P* = 0.007) and a higher median number of catheters in place (2 and 1, respectively; *P* = 0.02). Case patients were significantly more likely than the controls to have received care in an ICU (OR, 8.9; 95% confidence interval [CI], 2.2 to 36.2) or on a surgical service (OR, 7.5; 95% CI, 1.4 to 38.4), receive mechanical ventilation (OR, 13.0; 95% CI, 2.7 to 61.7) or TPN (OR, 5.9; 95% CI, 1.6 to 21.4), or have had a previous case of bacteremia or candidemia (OR, 3.8; 95% CI, 1.2 to 11.6) (Table 1).

TABLE 1. Univariate analysis of risk factors comparing all cases[a] and controls, hospital A, Mississippi, 2001

Risk factor	All cases ($n = 20$) and controls	
	OR[b]	95% CI
Any mechanical ventilation	13	2.7–61.7
TPN receipt	5.9	1.6–21.4
Mechanical ventilation on index day	10	1.9–51.3
ICU on index day	8.9	2.2–36.2
Surgical service	7.5	1.4–38.4
Previous bacteremia or candidemia	3.8	1.2–11.6

[a] Includes 13 confirmed cases and 7 possible cases, as 2 of the 15 confirmed cases were not included in the case-control study due to a lack of availability of medical records.
[b] The ORs presented are significant at the $P < 0.05$ level.

TABLE 2. Description of environmental and hand carriage samples obtained and culture results by type of sample, hospital A, Mississippi, 2001

Specimen cultured	No. (%) of samples:	
	Positive for *C. parapsilosis*	Obtained
Total HCW hand pairs	19 (28)	68
Nurses	14 (26)	53
Physicians	3 (43)	7
Other	2 (25)	8
CVC insertion sites	0	8
Medical device	1 (6)	16
Blood pressure cuff tubing	1 (13)	8
Electrocardiograph lead	0	8

The case patients were similar to the controls in terms of the type of indwelling vascular catheter (i.e., CVC, dialysis catheter, or peripherally inserted central catheter), the vessels in which the catheters were placed, the numbers of catheter lumens, the rates of dialysis, the numbers of major surgical procedures and nonsurgical procedures, and the numbers of medications received. Notably, the cases and the controls did not differ in the number or classes of antibiotics received or the receipt of fluconazole (55% of cases versus 35% of controls; $P = 0.14$). When we assessed the independent importance of each of these risk factors by multivariable analysis, concurrent hospitalization in an ICU (adjusted OR, 16.4; 95% CI, 1.8 to 148.1) and receipt of TPN (adjusted OR, 9.2; 95% CI, 0.9 to 98.1) were independently associated with an increased risk of being a case patient and were chosen as the most clinically relevant among the factors in predictive models.

Observational studies. We observed 79 hand hygiene opportunities during the three observation periods. A hand hygiene opportunity was defined as the time from HCW entry into a patient room until departure when the episodes included direct contact with the patient or with objects in the environment. Overall, hand hygiene was performed before contact in 30 (38%) opportunities and after contact in 39 (49%) opportunities. Among the opportunities involving direct patient contact, nurses performed hand hygiene before contact in 42% of 43 opportunities and after contact in 60% of 43 opportunities, and physicians performed hand hygiene before contact in 18% of 11 opportunities and after contact in 18% of 11 opportunities. Of 64 observed hand hygiene events, 45 (70%) were with an alcohol foam waterless agent, 16 (25%) were with antibacterial soap and water, and 3 (5%) were with both.

We found no deviations from protocol or breaks in aseptic technique during the preparation of TPN solutions, microbiology specimen preparation and handling, or placement and maintenance of CVCs.

Laboratory studies. We cultured swab specimens from the pairs of hands of 68 HCWs in the three ICUs, constituting 63% of the total ICU nursing staff (Table 2). Yeasts were recovered from 23 (34%) hand pairs; *C. parapsilosis* was recovered from 19 (28%) hand pairs, including those from 14 (26%) of 53 nurses, 3 (43%) of 7 physicians, and 2 (25%) of 8 other HCWs. *C. parapsilosis* was recovered from 1 (6%) of 16 cultures of specimens obtained from patient care devices (blood pressure

cuff tubing), but no yeasts were recovered from cultures of any of eight CVC hubs or insertion sites sampled.

Molecular typing of these isolates with the Cp3-13 probe (Fig. 2) demonstrated 15 isolates with DNA banding patterns related to one another at a value of 85%. This cluster included DNA from all 10 case-patient isolates collected during the outbreak period, 4 (67%) of 6 blood or CVC tip isolates collected after the outbreak period, and 1 (6%) of 17 isolates from the hands of HCWs (Fig. 2). The banding patterns of three other isolates from the hands of HCWs displayed 70% relatedness to this cluster. However, DNA from other hand and patient isolates, including the two epidemiologically unrelated patient isolates, displayed banding patterns with less significant (40 to 60%) degrees of relatedness. Subtyping with RAPD primers and by electrophoretic karyotyping gave consistent results (data not shown), but with a lesser degree of discrimination.

The antifungal susceptibility testing results for these isolates are shown in Fig. 2. The fluconazole MIC at which 50% of isolates are inhibited (MIC_{50}) for the 10 outbreak-related patient isolates was 4 µg/ml (range, 1 to 8 µg/ml). The MIC_{50} for the hand isolates was 0.5 µg/ml (range, 0.25 to 4 µg/ml). The fluconazole MICs for all 15 clinical and hand isolates in the predominant DNA cluster as well as the 3 less closely related hand isolates were between 1 and 8 µg/ml, with a median of 4 µg/ml. Fluconazole MICs for patient and hand isolates outside of this cluster were from 0.25 to 2 µg/ml. The voriconazole MICs, but not those of itraconazole, were similarly elevated for the isolates within the predominant DNA cluster. The median voriconazole MIC for this cluster was 0.25 µg/ml (range, 0.25 to 0.5 µg/ml), and the mean itraconazole MIC was 0.125 µg/ml (range, 0.06 to 0.125 µg/ml).

DISCUSSION

This paper describes the largest outbreak, to our knowledge, of *C. parapsilosis* BSIs reported among adults. The cause of this outbreak was multifactorial, resulting from the interplay of host, environment, and pathogen contributors. Case patients had severe illnesses requiring ICU care, mechanical ventilation, CVCs, and TPN use. These factors require frequent contact with HCWs, magnifying the impact of lapses in appropriate hand hygiene and facilitating cross-transmission of yeasts

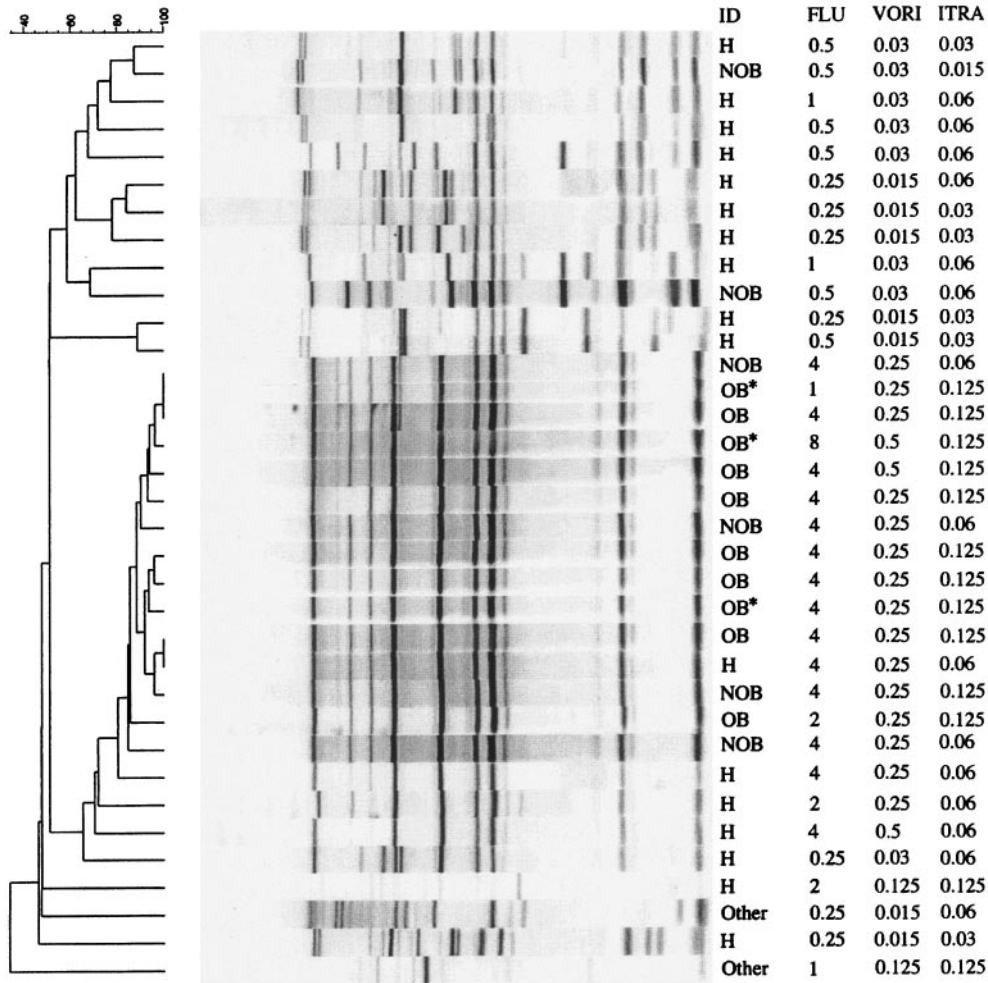| ID	FLU	VORI	ITRA
H	0.5	0.03	0.03
NOB	0.5	0.03	0.015
H	1	0.03	0.06
H	0.5	0.03	0.06
H	0.5	0.03	0.06
H	0.25	0.015	0.06
H	0.25	0.015	0.03
H	0.25	0.015	0.03
H	1	0.03	0.06
NOB	0.5	0.03	0.06
H	0.25	0.015	0.03
H	0.5	0.015	0.03
NOB	4	0.25	0.06
OB*	1	0.25	0.125
OB	4	0.25	0.125
OB*	8	0.5	0.125
OB	4	0.5	0.125
OB	4	0.25	0.125
NOB	4	0.25	0.06
OB	4	0.25	0.125
OB	4	0.25	0.125
OB*	4	0.25	0.125
OB	4	0.25	0.125
H	4	0.25	0.06
NOB	4	0.25	0.125
OB	2	0.25	0.125
NOB	4	0.25	0.06
H	4	0.25	0.06
H	2	0.25	0.06
H	4	0.5	0.06
H	0.25	0.03	0.06
H	2	0.125	0.125
Other	0.25	0.015	0.06
H	0.25	0.015	0.03
Other	1	0.125	0.125

FIG. 2. Cluster analysis results by Southern blotting with the Cp3-13 probe and testing for susceptibilities to fluconazole (FLU), voriconazole (VORI), and itraconazole (ITRA), hospital A, Mississippi, 2001. ID, type of isolate; H, hand; NOB, bloodstream or CVC tip isolates from patients after the outbreak period; OB, bloodstream or CVC tip isolates from case patients during the outbreak; OB∗, noninvasive isolates from case patients during the outbreak; Other, isolates from patients unrelated to the outbreak.

from transiently colonized HCW hands to patients. Finally, the *C. parapsilosis* outbreak cluster demonstrated reduced susceptibilities to the azole antifungals fluconazole and voriconazole, a property that may have promoted persistence on CVCs and patient skin in this environment where fluconazole is administered for antifungal treatment.

Lapses in compliance with hand hygiene practices may allow the transmission of *C. parapsilosis* from HCW hands to CVCs. Published data indicate that *C. parapsilosis* can be recovered from 5 to 26% of cultures of swab specimens from the hands of HCWs in surgical and neonatal ICUs in nonoutbreak settings (21). Moreover, the transmission of *C. parapsilosis* via the hands of HCWs has been implicated in a number of outbreaks (4, 13, 16, 22, 27). The rate of compliance with hand hygiene practices among HCWs at hospital A was similar to that reported in prior studies, which typically observe rates of compliance of less than 50% (20).

Analysis of the Cp3-13 fingerprint patterns showed that this outbreak was caused by a cluster of related isolates. One isolate from the hand of an HCW can be placed firmly in this

cluster, and three other hand isolates displayed lesser degrees of relatedness, although they still sorted within this cluster. The ability to discriminate among clinically relevant *C. parapsilosis* isolates has traditionally been limited due to similarities in electrophoretic karyotypes and RAPD profiles between strains and a lack of interlaboratory reproducibility among methods. The high degree of variability between strains demonstrated with the Cp3-13 probe has allowed us to discriminate among related isolates and to demonstrate a specific fingerprint profile among outbreak isolates.

Once the outbreak *C. parapsilosis* cluster was introduced onto catheters from HCW hands, several properties of the cluster may have promoted survival and introduction of the isolates into the bloodstreams of the case patients. Solutions that contain high concentrations of glucose and amino acids, such as TPN, confer a selective growth advantage to *Candida* species, including *C. parapsilosis* (8, 9, 23). Furthermore, several isolates from this outbreak cluster have been shown to form biofilms in vitro (14). *C. parapsilosis* is known to form extensive biofilms on bioprosthetic materials, and biofilm for-

mation can confer relative resistance to antifungal drugs (2). Finally, reduced susceptibility to fluconazole and its derivative voriconazole, but not the structurally distinct antifungal itraconazole, may have promoted propagation and infection. While the MIC for this bloodstream cluster does not approach the cutoff value for resistance to fluconazole (MIC > 32 μg/ml), the median MIC of 4 μg/ml is unusual, as *C. parapsilosis* isolates typically exhibit extreme susceptibility to fluconazole (11). In this institutional setting of prior fluconazole use (55% of case patients and 35% of control patients had previously received fluconazole), such variance in susceptibility may provide an ecologic advantage over other skin and CVC hub flora and allow this yeast to remain viable in the local environment. The relative roles of these phenotypic factors in the epidemiology and pathogenesis of *C. parapsilosis* remain to be investigated, but the ability to correlate various molecular subtypes with unusual phenotypic properties will be useful.

As a result of this investigation, hospital A created a multidisciplinary program, with hospital administration support, designed to improve HCW adherence to recommended hand hygiene practices. The indications for hand hygiene were expanded, as outlined in the Hospital Infection Control Practices Advisory Committee hand hygiene guideline (7). In addition, fluconazole use practices in the ICUs were reviewed. Subsequent to the interventions, the number of cases of *C. parapsilosis* BSIs at hospital A diminished. Outbreak cluster isolates were still recovered from blood and CVC tips after the conclusion of the outbreak period; however, they were not of the single fingerprint type found to cause invasive disease among hospitalized patients.

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