

Investigation of *Candida albicans* Transmission in a Surgical Intensive Care Unit Cluster by Using Genomic DNA Typing Methods

ANDREAS VOSS,¹† MICHAEL A. PFALLER,^{2*} RICHARD J. HOLLIS,² JANET RHINE-CHALBERG,³
AND BRADLEY N. DOEBBELING^{1,4}

Department of Internal Medicine, Division of General Medicine, Clinical Epidemiology and Health Services Research,¹
and Department of Pathology, Division of Microbiology,² The University of Iowa College of Medicine, Iowa City,
Iowa 52242; Department of Pathology, Oregon Health Sciences University, Portland,
Oregon 97201³; and Veterans Affairs Medical Center, Iowa City, Iowa 52246⁴

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An apparent outbreak of serious *Candida albicans* infections ($n = 6$) occurred in a surgical intensive care unit over a 4-week period. Four patients developed *C. albicans* bloodstream infections. An additional patient developed catheter-related *C. albicans* infection; the sixth patient developed an infection of cerebrospinal fluid. *C. albicans* was isolated from the hands of five health care workers (17%) and the throat of one health care worker (3%) during the outbreak investigation. Karyotyping and restriction endonuclease analysis of genomic DNA with *Bss*HII of 23 *C. albicans* isolates from patients and the 6 health care worker isolates revealed 9 and 12 different patterns, respectively. Three of six patients appeared to be infected with the same *C. albicans* strain (two bloodstream infections and one cerebrospinal fluid infection). The hands of a health care worker were colonized with strain that appeared identical to an isolate from a patient prior to infection of the patient. However, restriction endonuclease analysis with *Sfi*I found differences among the isolates determined to be identical by the other two methods. Karyotyping alone does not appear to be sufficient to differentiate between outbreak and control isolates. Restriction endonuclease analysis typing may be a more sensitive method than karyotyping alone in the investigation of a cluster of *C. albicans* infections. Furthermore, the use of more than one restriction enzyme may be necessary for optimal strain discrimination in restriction endonuclease analysis of genomic DNA.

In recent years, the *Candida* spp. have emerged as important nosocomial pathogens. Over the past decade, the incidence of *Candida* bloodstream infections increased by 219 to 487% in U.S. teaching hospitals and by 75 to 370% in nonteaching hospitals (1, 21). Candidemia occurs most frequently in immunocompromised patients with an underlying malignancy or hematological disorder (14, 15) and in severely ill burn patients, as well as surgical intensive care unit (SICU) and neonatal intensive care unit (ICU) patients (3-5, 18, 23, 26). Therefore, incidence rates of candidemia are highest in tertiary care referral hospitals. The incidence rate at the University of Iowa Hospitals and Clinics is 8.5 per 10,000 admissions, with 57% crude and 38% attributable mortalities (30).

Until recently, the development of invasive *Candida* infections was thought to be more or less exclusively due to autoinfection by endogenous *Candida* strains which initially colonize the patient. Using molecular typing methods, investigators have confirmed this hypothesis in neutropenic and nonneutropenic patients (20, 25, 27). However, exogenous sources responsible for outbreaks have been described increasingly, including cross-infection among ICU patients attributed to hand carriage by health care workers (HCWs) (3, 12), contaminated medications, pressure transducers, parenteral nutrition, and reused disposable devices (16, 22, 24, 28, 29, 31). In half of such outbreaks reviewed by Sherertz et al. (22), the source could not

be identified, possibly because of the lack of reliable and readily available typing methods for *Candida* spp.

We report an outbreak of systemic *Candida albicans* infections in an SICU in which apparently identical isolates were recovered from three patients' sites of infection and from the hands of an HCW, prior to development of infection in one of the patients. The epidemiology of the carriage and transmission of *C. albicans* among patients in the SICU was further clarified by the application of molecular typing methods.

MATERIALS AND METHODS

Hospital and patients. The University of Iowa Hospitals and Clinics is a 901-bed teaching hospital and tertiary care referral center, with approximately 200 beds designated for intensive care. The SICU (Fig. 1) at the time of the cluster of infections was divided into four bays with a total of 24 beds. The nurse-to-patient ratio ranged from 1:2 to 1:1, depending on the patients' needs and availability of nursing staff. A mean of 164 patients per month (standard deviation, ± 12) were admitted to the SICU during the 9 months prior to the outbreak. During the 4-week period of the outbreak, 163 patients had been admitted to the SICU. The unit is prospectively surveyed by trained infection control nurses each weekday. Additionally, the surveillance system has been prospectively validated recently (2). No significant changes in personnel, equipment, or infection control surveillance or definitions occurred during the outbreak period or in the previous 9 months.

Outbreak description. During the period of the cluster, the observed rate of *C. albicans* bloodstream infections exceeded the upper limit of the predicted 95% confidence interval, and an outbreak investigation was initiated. Microbiological data, infection control surveillance data, and clinical information for all patients were reviewed in search of a common source or vehicle. In order to determine current rates of carriage among SICU workers, the hands and throats of 30 HCWs were sampled prospectively at random intervals over the next 2 weeks by using the broth-bag technique (19) and sterile premoistened rayon-tipped swabs (Culturette II; Marion Scientific, Kansas City, Mo.), respectively. Pressure transducers of patients receiving intra-arterial monitoring and the ward stock insulin in use were also cultured. Similarly, the throats and stools of patients in the SICU over the 5 weeks following the identification of the outbreak were also cultured at random intervals. All *Candida* isolates were banked and identified to the

* Corresponding author. Mailing address: 273 MRC, Department of Pathology, University of Iowa College of Medicine, Iowa City, IA 52242. Phone: (319) 335-8170. Fax: (319) 335-8348.

† Present address: Department of Medical Microbiology, University Hospital Nijmegen, St. Radboud, 6500 HB Nijmegen, The Netherlands.

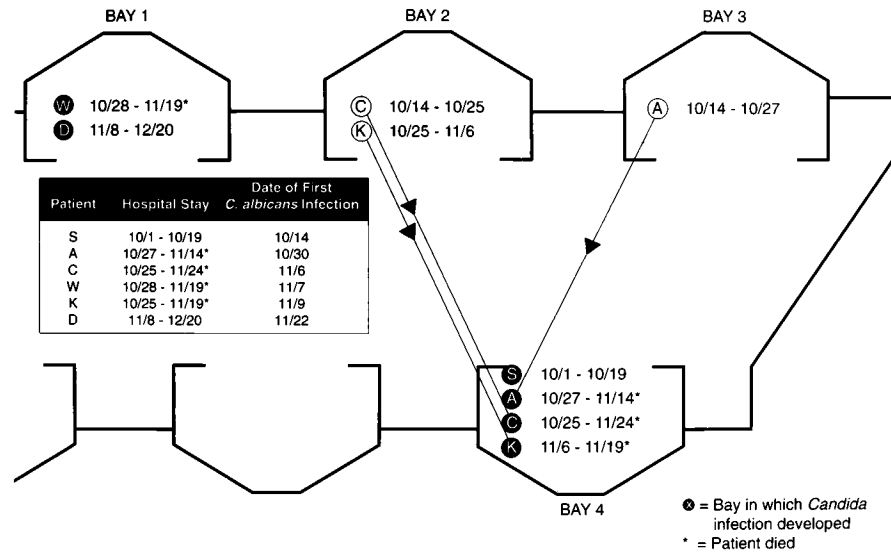


FIG. 1. Schematic diagram of bays 1 to 4 of the SICU, showing the initial localization and transfer of the cluster patients.

species level by using the API 20C system (Analytab Products, Plainview, N.Y.). Cases were identified by reviewing microbiology reports and patient data from charts and the hospital's mainframe computer and data gathered by infection control nurses. The importance of hand washing and compliance with the guidelines for prevention of nosocomial infections were reemphasized at the time of the identification of the cluster.

Molecular typing. Molecular typing of all isolates was accomplished by electrophoretic karyotype (EK) analysis and by restriction endonuclease analysis of genomic DNA (REAG) using the restriction enzymes *Bss*HII (REAG-B) and *Sfi*I (REAG-S) followed by pulsed-field gel electrophoresis. Electrophoretic karyotyping and REAG were performed as described previously (6, 8, 27).

Analysis. EK and REAG profiles were analyzed by visual inspection of photographs of ethidium bromide-stained gels. Photographs were analyzed to detect similarities and differences in banding patterns by three observers who were blinded to the origin of the isolate and the results of the other observers. Isolates were considered identical when all of the bands matched, similar when $\geq 95\%$ but $< 100\%$ of the bands matched, and different when $< 95\%$ of the bands matched. Interobserver reliability was calculated by using the kappa coefficient (32).

RESULTS

Patients. Between 14 October and 22 November 1990, a total of six serious *C. albicans* infections occurred in an open SICU ward with adjacent beds, in which patients were close together and often cared for by the same HCW (Fig. 1). Four of the six patients had candidemia, one had a catheter-related infection, and one had a central nervous system infection. The incidence density ratio for candidemia during the outbreak period was significantly elevated: 4 infections per 577 patient days versus 4 per 6,430 patient days in the entire year (incidence density ratio, 11.1; 95% confidence interval, 2.79 to 44.56). Similarly, the incidence density rate difference was 0.0063 (95% confidence interval, 0.0005 to 0.01). The underlying diseases and risk factors for infection of the six patients involved in the cluster are shown in Table 1. Four patients had undergone abdominal surgery, and five had diabetes mellitus as their major underlying disease. Risk factors for infection included intravascular catheters for six patients, five or more antibiotics for five patients, and total parenteral nutrition for four patients (Table 1).

Microbiological surveillance. Following identification of the cluster, the hands and throats of 30 different HCWs were cultured. Seventeen percent of the hand cultures and 33% of the throat cultures of HCWs yielded *C. albicans*. At the same

time, the throats of 33% of the patients and the stools of 15% of the patients were colonized with *C. albicans*. In the subsequent 3 weeks, rates of *C. albicans* colonization among patients were 30 and 12% for the throat and stool, respectively. This difference was not statistically significant ($P > 0.20$).

Molecular typing. In the analysis of the DNA profiles of the isolates, a high degree of interobserver reliability was observed: the generalized kappa statistics were 0.84 or greater for EK and REAG-B and REAG-S profiles ($P < 0.001$ for each). The results of the overall interpretation (consensus call of the three observers) are given in Table 2.

A total of 20 isolates from six outbreak patients (patients S, A, W, D, C, and K), the hand isolates from the five HCWs with positive cultures, and isolates from two additional SICU patients (patients 1 and 2) colonized with *C. albicans* following the outbreak were typed by all three methods. EK analysis and REAG-B and REAG-S identified 9, 10, and 10 different patients, respectively (Table 2 and Fig. 2 to 4). The combination

TABLE 1. Underlying diseases and risk factors of the SICU cluster patients

Risk factor	Presence of factor for patient:					
	S	W	K	C	A	D
Infection ^a						
CRI	+					
CSF		+				
BSI			+	+	+	+
Intravascular catheter						
Central venous	+	+	+	+	+	+
Arterial line	+	+	+	+	+	+
Peripheral line	+	+	+	+	+	+
No. of antibiotics						
≤ 4	+					
≥ 5		+	+	+	+	+
TPN ^b	+			+	+	+
Abdominal surgery	+			+	+	+
Diabetes mellitus	+	+	+		+	+

^a CRI, catheter-related infection; CSF, cerebrospinal fluid; BSI, bloodstream infection.

^b TPN, total parenteral nutrition.

TABLE 2. Summary results of karyotyping and REAG

Patient or HCW	Isolate no.	Origin	Karyotype	REAG-B type ^a	REAG-S type ^a
S	1	Catheter	A	1a	I
	2	Catheter	A	1a	I
A	3	Blood	A	1b	II
	4	Blood	A	1a	II
	5	Urine	A	1c	II
	6	Urine	A	1c	II
	7	Urine	A	1c	II
W	8	Blood	A	1c	II
	9	CSF ^b	B	2	IIIa
	10	Trachea	B	2	IIIa
D	11	CSF	B	2	IIIa
	12	Blood	A	3	IIIa
HCW 1	13	Eye	C	4	IV
	14	Hand	A	1c	V
C	15	Throat	A	1c	VI
	16	Catheter	D	5	IIIb
K	17	Blood	D	5	IIIb
	19	Catheter	D	5	IIIb
	20	Trachea	D	5	IIIb
	21	Trachea	A	3	IV
Patient	22	Blood	E	5	V
	23	Trachea	A	3	IV
	24	Sputum	E	6	VI
HCW 2	25	Trachea	F	7	VII
HCW 3	26	Hand	C	8	IV
HCW 4	27	Hand	G	9	VIII
HCW 5	28	Hand	H	10	IX
	29	Hand	I	1c	X

^a Lowercase letters indicate subtypes with ≥95% but <100% matching bands.
^b CSF, cerebrospinal fluid.

of all three methods (composite DNA type) identified 16 different profiles.

Identical EK patterns (EK A) were obtained for all isolates from patients S and A and from the hands and throat of HCW 1. Additionally, EK A was found in the blood and trachea of patients D and K, respectively (Table 2). In contrast, distinctly different EKs were observed for isolates from patients W and C, SICU patients 1 and 2, and HCWs 2 to 5 (Table 2). For six of the seven individuals with two or more isolates of *C. albi-*

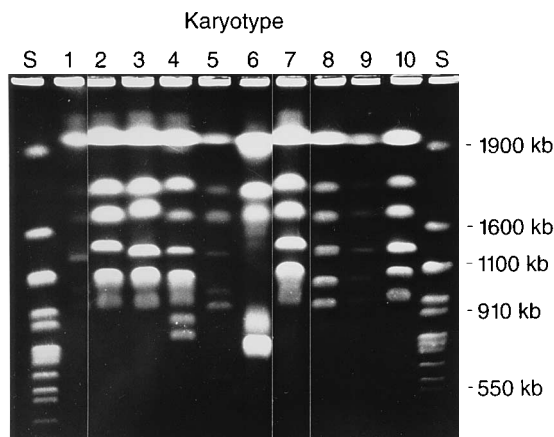


FIG. 2. Representative EK profiles of *C. albicans*. Lanes: S, *Saccharomyces cerevisiae* chromosome DNA size standards (sizes are indicated on the right); 1, *C. albicans* control strain; 2 and 3, EK E; 4, EK H; 5, EK F; 6, EK G; 7, EK D; 8 to 10, EK A.

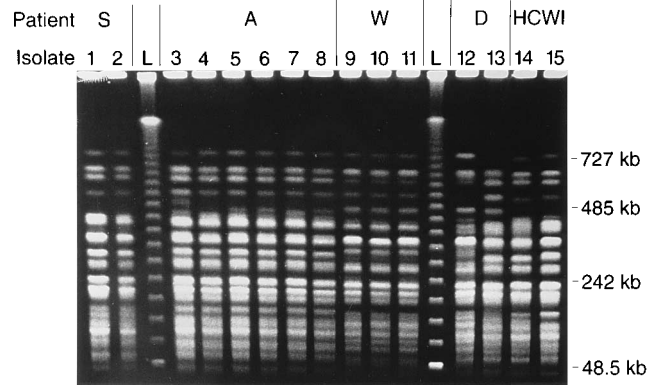


FIG. 3. Types of *C. albicans* obtained by REAG-B followed by pulsed-field gel electrophoresis. Results are shown for blood culture and other-site isolates from patients S, A, W, and D and HCW 1. Lane numbers correspond to the isolate numbers in Table 2. Banding patterns of isolates from patients S and A and HCW 1 represent identical or closely related subtypes (≥95% of bands are shared). Lanes L, molecular size standards (lambda phage DNA concatemers; sizes are indicated on the right).

cans, the same EK was observed on more than one occasion and/or for specimens from more than one anatomic site.

The relationship among isolates determined by REAG-B generally supported that determined by EK analysis (Table 2). All isolates from patients S and A and HCW 1 had the same basic REAG-B profile (type 1), allowing for minor banding differences (shared ≥95% of bands; Fig. 3). REAG-B also found the blood and tracheal isolates from patients D and K to be identical (type 3) but different from the isolates of patients S, A, and HCW 1 despite a common EK (Fig. 3). As with EK analysis, the isolates from patients W and C, SICU patients 1 and 2, and HCWs 2 to 5 were all different as determined by REAG-B. Likewise, REAG-B demonstrated that multiple isolates from the same patient generally had the same DNA banding pattern (Fig. 3).

In contrast to the findings with EK analysis and REAG-B, REAG-S identified differences among the outbreak isolates (Table 2 and Fig. 4). Specifically, isolates from patients S and A and HCW 1 each had a different REAG-S profile despite having the same EK and REAG-B types (Table 2 and Fig. 3

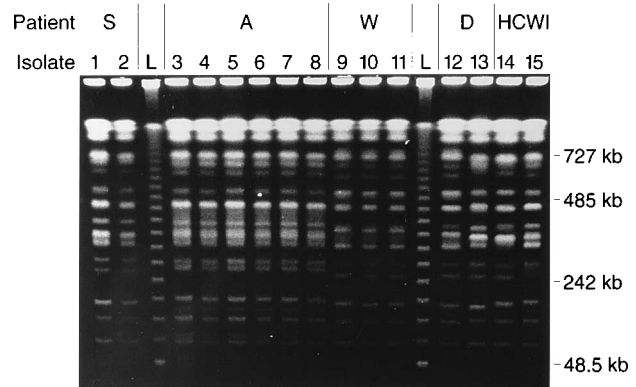


FIG. 4. Types of *C. albicans* obtained by REAG-S followed by pulsed-field gel electrophoresis. Isolates are the same as for Fig. 3. Differences in banding patterns are seen among isolates from patients S and A and HCW 1, as well as patients W and D. Lanes L, molecular size standards (lambda phage DNA concatemers; sizes are indicated on the right).

and 4). Several patients had the same REAG-S profile: REAG-S type III was shared by patients W, D, and C; type IV was shared by patients D and K and HCW 2; type V was shared by HCW 1 and patient K; and type VI was shared by HCW 1 and patient 1 (Table 2). However, these isolates were identified as different strains on the basis of REAG-B or EK analysis (Table 2). As with the other typing methods, multiple isolates from the same patient generally had the same REAG-S profile.

When the results of all three typing methods were considered (composite DNA type), a total of 16 DNA types were identified among 27 isolates from 13 individuals (Table 2). None of the composite DNA types were shared by two or more individuals. Patients S, A, W, and C each maintained their own unique DNA type of *C. albicans* over time and from multiple anatomic sites, whereas patients D and K and HCW 1 each had two different DNA types colonizing or infecting different anatomic sites.

DISCUSSION

One of the important considerations regarding the prevention and control of nosocomial candidiasis is whether the infection is endogenous or exogenous to the patient (17). It is reasonable to assume that endogenous forms of infection may require strategies for prevention (e.g., antifungal prophylaxis) which are different from those for exogenous infections due to transmission of any organism from patient to patient (hand washing and other infection control measures). Our understanding of this area is still evolving; however, the use of molecular typing methods to fingerprint *Candida* species has been very useful in epidemiologic studies designed to address these issues (6, 20, 22, 24, 27).

The evidence for endogenous candidal infection in hospitalized patients includes the findings that unique strains of *Candida* are usually seen for each patient, that the same *Candida* DNA type is usually isolated from multiple anatomic sites over time, that colonizing and infecting strains are usually the same DNA type, and that the colonizing isolate usually precedes the infecting isolate (20, 27).

Despite the importance of endogenous infection, there are now several reports documenting transmission of *Candida* species from patient to patient, particularly in the ICU setting (3, 10, 12, 23, 26). The open nature of many ICUs and the level of activity make it difficult to implement or enforce infection control practices, thus facilitating nosocomial transmission of pathogenic organisms such as *Candida* spp. Evidence for carriage of the infecting strain of *Candida* on the hands of HCWs is mounting, suggesting that simple hand washing may be an effective infection control measure (6, 7). Unfortunately, compliance with hand-washing policies among HCW personnel is less than optimal and underscores the problem of controlling nosocomial transmission of *Candida* and other pathogens (9).

In the present study, we investigated a cluster of *Candida* infections in a single ICU in which surveillance cultures indicated hand carriage by several HCWs of the same species of *Candida* (*C. albicans*) carried by the infected patients. The clustering of these infections in time and space coupled with hand carriage of the infecting species suggested the possibility of nosocomial transmission. The epidemiology was clarified by the use of DNA-based typing methods, including EK analysis and REAG-B and REAG-S.

Application of EK analysis alone suggested infection of four patients and colonization of one HCW with a single strain of *C. albicans*. Two additional patients shared a second EK of *C. albicans*, and the remaining patients and HCWs were each colonized with their own unique EK. This relationship among

isolates and patients was corroborated by REAG-B. Importantly, apparently the same strain eventually causing infection in a previously uninfected patient was identified on the hands of an HCW prior to development of infection in that patient. Isolates from two patients and one HCW had the same EK and REAG-B type, suggesting limited nosocomial transmission of a single strain of *C. albicans* and linking the HCW to the two infected patients.

One of the major tenets of epidemiologic typing is that although one or more typing methods may be used to demonstrate convincingly that two nosocomial pathogens are different from one another, it is very difficult to prove that they are the same strain. To this end, epidemiologic typing systems are used in combination to enhance discrimination among bacterial isolates. However, this combined approach has been used infrequently for *Candida* species. Previously, Hunter and Fraser (11) have demonstrated enhanced discriminatory power for typing isolates of *C. albicans* with the combination of restotyping and morphotyping, suggesting that two or more methods employed in parallel or in a hierarchical fashion may be necessary for epidemiologic studies of *C. albicans*. More recently, Mercure et al. (13) demonstrated enhanced discrimination among *C. albicans* strains, using two DNA-based typing methods, restriction fragment length polymorphism analysis and Southern hybridization with DNA probe 27A. In the present study, further analysis of the *C. albicans* isolates with a second restriction enzyme, *Sfi*I, identified differences among the isolates with identical EK and REAG-B profiles, indicating that they may not be clonally related. The combination of EK analysis and REAG with two enzymes revealed unique DNA profiles for isolates from each patient and HCW. No two isolates from patients or HCWs shared all of the DNA markers.

Despite the great heterogeneity among DNA types generated by the composite (EK, REAG-B, and REAG-S) typing approach, the ability of this approach to identify related strains within an individual patient remained intact. Although we observed three individuals infected or colonized by two strains of *C. albicans*, the overall pattern was similar to that described previously (20, 27) in that patients with multiple isolates were generally colonized and infected by a single strain of *C. albicans* that persisted over time at multiple anatomic sites. Overall, five of the six patients in this study were found to be infected or colonized by their own unique strain on two or more occasions.

In summary, distinct DNA types of clinical isolates of *C. albicans* were identified by using a composite approach of electrophoretic karyotyping and REAG with two different restriction enzymes. The combination improved strain discrimination compared with that of any one of the typing methods used alone. Epidemiologic investigation demonstrated that an individual patient usually harbored a single composite DNA type of *C. albicans* that was not shared with those of other patients or HCWs. These findings speak against nosocomial transmission of a single strain as a cause of the entire cluster of *C. albicans* infections. The fact that isolates from patients S and A and HCW 1 had the same strain of *C. albicans* as determined by two of the three molecular typing approaches (EK analysis and REAG-B) suggests that some transmission may have occurred on a small scale. Differences observed with the third typing approach (REAG-S) may reflect the propensity for *C. albicans* to undergo genomic rearrangements and suggests that although these isolates may have had a common origin, direct patient-to-patient or HCW-to-patient transmission is unlikely. Molecular typing methods may be used effectively to clarify the epidemiology of nosocomial infections; however, the various typing methods must be used with the

understanding that more than one approach may be necessary to achieve optimal strain discrimination.

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