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Characterization of *Candida* Isolates from Pediatric Burn Patients

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To provide more detailed information about *Candida* epidemiology and pathogenesis in pediatric burn patients, *Candida* isolates from 113 patients collected over 3 years were identified at the species level and the serotypes and biotypes of the *C. albicans* isolates were determined. A total of 85% of the patients were colonized or infected by *C. albicans*, 18% by *C. tropicalis*, and 11% by *C. parapsilosis*. Although colonization or infection often was found at multiple sites and times, 87% of the patients were colonized or infected by only one *Candida* species or strain; the other 13% showed multiple colonizations or infections, some of which occurred simultaneously at the same site. *C. albicans* biotyping determined the tolerance of the isolates to pH (pH 1.4) and salt; flucytosine, borate, and safranine resistance; and ability to produce proteinase and assimilate urea, sorbose, and citrate; results are expressed as three-digit numbers. For isolates from three different anatomical sites, the distribution of the nine biotype characteristics was similar in all cases but one. Significantly more fecal than wound or throat isolates were resistant to safranine. Sixty-four different serotype-biotype combinations were found in the 96 patients with *C. albicans* infections or colonizations. Twenty-nine percent of all *C. albicans* isolates had the partial biotype -57, while 20 of the 96 patients had specifically serotype B, biotype 557 colonizations or infections. Eleven patients had the B557 infection when admitted; nine patients acquired the yeast in-house. Thirty percent of the *C. albicans* isolated from 23 adult patients at a nearby hospital also showed the -57 biotype pattern, suggesting that *C. albicans* isolates expressing this biotype are either extremely prevalent in nature or are more virulent than other *C. albicans* isolates.

Several *Candida* species are secondary pathogens which, with the use of topical and systemic antibiotics to suppress bacteria, have become reponsible for a growing number of deaths in burn patients (1, 5, 6, 9, 16, 23). While these fungi are often cultured from burn wounds and are frequently innocuous, there are times when *Candida* infection becomes invasive and life-threatening. Spebar and Pruitt (23) have reported that of 172 patients with *Candida* colonization of the eschar, only 20.7% subsequently developed invasive candidal sepsis. However, once fungal sepsis occurs in burn patients, over 90% of these individuals die (1, 16, 23). To combat the high mortality, prevention of the invasive stage of infection by expeditious closure of the burn wound has been suggested (16, 23), and treatment with antifungal agents has been used (4–6, 16). However, the systemic antifungal agents themselves are toxic to the patient (4, 6). Hence, *Candida* sepsis continues to persist as a significant problem for burn (16) and other immunocompromised (2, 5, 9, 17) patients.

Since candidiasis is so difficult to treat, an active program of prevention of the infection may be an effective way to attack this disease. The formulation of such a program, however, requires detailed information about *Candida* pathogenesis and epidemiology in burn patients (17). Information about *C. albicans* would be of prime importance, since this species is the one most often cultured from burn patients (1) and, in general, is considered to be the most virulent (11). Until recently, however, detailed study of the sources, modes of transmission, and types of *C. albicans* in the causation of candidiasis has not been possible because of the absence of a method for fine subdivision of strains within the species; hence, one *C. albicans* could not be distinguished from another. Earlier this decade, Odds and Abbott (12, 13) presented a system for the differentiation of *C. albicans* strains based on the growth of the yeast on nine differential media, thus allowing, in theory, 512 strain types or biotypes to be distinguished. The purpose of the present study was to address the occurrence in burn patients of *Candida* species, in general, and *C. albicans* isolates, in particular, thereby obtaining more detailed information about *Candida* epidemiology and pathogenesis in this patient population.

MATERIALS AND METHODS

Isolates. *Candida* isolates were obtained from 113 pediatric burn patients at the Shriners Burns Institute, Cincinnati Unit (Cincinnati, Ohio), from October 1983 to January 1987, and from 23 adult nonburn patients at University Hospital (Cincinnati, Ohio) from October 1981 to January 1987. The yeasts were isolated from wounds, stools, blood, intravenous catheter tips, throat and oral cavities, tracheas and sputa, urine catheters, peritoneal fluid, and cerebrospinal fluid. *Candida* species isolated within the first 5 days of patient admission were considered to have been brought in with the patient, while any isolates found after the initial 5 days of hospitalization were arbitrarily defined as acquired within the hospital. Yeasts were identified as *C. albicans* based on the production of germ tubes on incubation for 2 h in bovine serum and on growth of the yeasts on a pH 1.55 agar (12). *C. tropicalis* and *C. parapsilosis* were identified based on clinical yeast system tests (API 20C; Analytab Products, Plainview, N.Y.; and Vitek Systems, Inc., Hazelwood, Mo.). Microscopic morphology was studied by using rice extract and cornmeal agars. Isolates were stored at −70°C in skim milk-brain heart infusion broth, streaked onto Sabouraud dextrose agar slants for revival, and then grown

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TABLE 1. Distribution of species in 113 pediatric burn patients colonized by single or multiple *Candida* species

Species isolated	No. of patients
C. albicans only	82
C. tropicalis only	11
C. parapsilosis only	6
C. albicans and *C. tropicalis*	8
C. albicans and *C. parapsilosis*	5
C. albicans, *C. tropicalis*, and *C. parapsilosis*	1

on yeast nitrogen base-glucose agar immediately before biotypes were determined.

Biotyping and serotyping. Isolates were biotyped in the laboratory of F. C. Odds by using the typing system described previously (12) and modified (13) by Odds and Abbott. Briefly, this system differentiates among isolates of *C. albicans* based on the growth of the yeasts on nine differential media. For scoring, the nine tests were divided into the following three groups. Group 1 assayed pH 1.4 tolerance, proteinase production, and flucytosine resistance; group 2 screened for urea assimilation, sorbose assimilation, and salt tolerance; group 3 examined citrate assimilation, borate resistance, and safranine resistance. No growth on a test plate was scored as 0. Growth on the first medium in each group was scored as +1, growth on the second medium in each group was scored as +2, and growth on the third medium in each group was scored as +4. For each group of tests, a single number was generated by adding the score for all positive test results within the group. Thus, from the three groups, a three-digit number resulted. This number, designated the biotype, describes the growth pattern of the isolate on all nine tests. Hence, a biotype of 531 indicates an isolate which grew at pH 1.4; was resistant to flucytosine; and assimilated urea, sorbose, and citrate; but did not grow under the other four media conditions. Closely similar isolate results were shown by recording the two different biotype digits separated by a slash. For example, biotype 153/7 indicates that either biotype 153 or 157 was found. Previous studies have shown that the biotyping tests are reproducible within ±1 test difference (12); hence, for the drawing of conclusions in this study, isolates were considered different only if they differed in three or more of the biotyping tests or if they had different serotypes. For biotyping, the isolates were coded, run blindly in triplicate on the nine test plates in three batches, and interpreted by the same person.

C. albicans serotypes were distinguished on the basis of reactions of agglutination (serotype A) or nonagglutination (serotype B) with *Candida*-check antiserum 6 (Iatron Inc., Tokyo, Japan). All serotyping was also done blindly.

Statistical analyses. Significance of differences in the number of isolates showing a certain biotype characteristic was determined by 2 by 2 chi-square tests with Yates correction for continuity (21). Differences were considered significant at $P < 0.05$.

RESULTS

Three different *Candida* species were isolated from the 113 pediatric burn patients. The number of patients with single or multiple *Candida* species colonizations are listed in Table 1. Most patients (99 of 113) were colonized by only one species; that species was often found at several sites over several days (Table 2, patient A). In 14 of the 113 patients, different *Candida* species occurred at the same time and sometimes even at the same site (Table 2, patients B and C). In one case, *C. albicans*, *C. tropicalis*, and *C. parapsilosis* were isolated from the same patient at the same time (Table 2, patient C).

TABLE 2. Multiple serotype and biotype determinations for seven pediatric burn patients

Patient	Date of isolation (mo/day/yr)	Site of isolation	Species/serotype and biotype
A	3/29/85	Stool	*C. tropicalis*/ND[a]
	4/1/85	Back	*C. tropicalis*/ND
	4/6/85	Blood	*C. tropicalis*/ND
	4/8/85	Shoulder	*C. tropicalis*/ND
B	3/17/85	Stool	*C. albicans*/B557 + 104[b]
	3/17/85	Stool	*C. tropicalis*/ND
	3/17/85	Scalp	*C. albicans*/A477
	3/18/85	Flank	*C. albicans*/A657
	3/27/85	Leg	*C. albicans*/A557
C	10/23/85	Throat	*C. albicans*/B373
	10/23/85	Throat	*C. parapsilosis*/ND
	10/23/85	Stool	*C. albicans*/B355
	10/23/85	Stool	*C. tropicalis*/ND
D	10/7/83	Throat	*C. albicans*/A353
	10/7/83	Face	*C. albicans*/A353
	10/9/83	Intravenous tip	*C. albicans*/A153
	10/13/83	Trachea	*C. albicans*/A153
	11/8/83	Right arm	*C. parapsilosis*/ND
	11/10/83	Left arm	*C. albicans*/A353
	11/19/83	Thigh	*C. albicans*/A353
E	3/4/86	Throat	*C. albicans*/A317
	3/10/86	Throat	*C. albicans*/A317
	3/10/86	Throat	*C. albicans*/B577
F	11/10/83	Chest	*C. parapsilosis*/ND
	11/28/83	Hand	*C. parapsilosis*/ND
	1/6/84	Arm	*C. albicans*/A155
	1/16/84	Ear	*C. parapsilosis*/ND
G	4/30/85	Flank	*C. albicans*/A177
	5/2/85	Intravenous tip	*C. albicans*/A157
	5/2/85	Leg	*C. albicans*/A157
	5/2/85	Blood	*C. albicans*/A157
	5/18/85	Foot	*C. albicans*/A157
	11/2/86	Left hand	*C. albicans*/A133
	11/2/86	Left hand	*C. albicans*/A233

[a] ND, Not determined.
[b] *C. albicans* biotype 104 was not serotyped.

Serotypes of 157 *C. albicans* isolates from 96 pediatric burn patients were determined; 105 isolates were serotype A and 52 were serotype B. For 31 of the 96 patients colonized by *C. albicans*, more than one *C. albicans* culture was obtained. For 28 of these patients, the same *C. albicans*, by our criteria, was found repeatedly, as illustrated by patient D (Table 2). For three patients, however, more than one *C. albicans* was isolated, sometimes even from the same site, as exemplified by patient E (Table 2) who, on 10 March 1986, had both a serotype A, biotype 317 *C. albicans* and a serotype B, biotype 577 *C. albicans* isolated from his throat.

A total of 64 different serotype-biotype number combinations were found in the isolates from the 96 pediatric burn patients (Table 3). Over one-half (50%) of the serotype-biotype combinations appeared only once. A total of 29% of

TABLE 3. Serotypes and biotypes of 128 *C. albicans* isolates from 96 pediatric burn patients

No. (%) of different patients with the serotype and biotype	Serotype and biotype
1 (0.8)	A015, A057, A076, A077, 104,[a] A137, A155, B155, A171, A173, A211, A236, A237, A275, A277, A313, A333, A335, A337, B377, B417, A457, B457, A473, A477, B477, B513, B515, B517, B553, B571, A577, A657, B657, A677, A777, B777
2 (1.6)	A037, A053, A113, A135, A233, A311, A351, B373, A377, A557, B757
3 (2.3)	A013, A117, A133, A153, B157, A213, A217, A315, A317, B355, A373, B577
4 (3.2)	A177, A353
5 (3.9)	A157
20 (15.6)	B557

[a] The serotype for strain 104 was not determined.

all isolates showed similar biotype test results for the second and third three-set tests, giving the partial biotype of −57, and 16% of the 128 isolates were specifically serotype B, biotype 557. Of the 20 patients with serotype B, biotype 557 infections, 11 were admitted to the hospital with the infection, while 9 patients acquired the yeast after admission.

The results of individual biotyping tests performed on isolates from throats, wounds, or stools of pediatric burn patients are compared in Table 4. With the exception of safranine resistance, any single biotype characteristic was quite consistent from one isolation site to another. Safranine was significantly more inhibitory to isolates from wounds and throats than it was to isolates from stools.

To determine whether the serotyping-biotyping patterns of isolates from these pediatric burn patients differed significantly from the patterns of isolates from patients in the local adult nonburn population, biotypes of 27 isolates from 23 adult patients at another local hospital were determined. Of these isolates, 14 were serotype A and 13 were serotype B. Twenty-one different serotype-biotype combinations were found; 30% of these isolates had the -57 biotype pattern (Table 5). When results for individual biotype characteristics between the two patient populations were compared, isolates from both populations were found to be very similar,

TABLE 4. Variations in percentage of biotype characteristics in isolates from throats, wounds, and stools of pediatric burn patients

Characteristic	% Biotype characteristics in isolates from:		
	Throat (n = 43)	Wound (n = 50)	Stool (n = 28)
pH 1.4 tolerance	74	74	93
Proteinase production	40	34	32
Flucytosine resistance	44	38	36
Urea assimilation	100	100	96
Sorbose assimilation	33	34	18
Salt tolerance	70	68	75
Citrate assimilation	100	98	96
Boric acid resistance	93	82	75
Safranine resistance[a]	65	70	96

[a] The stool isolates were significantly more resistant to safranine than were the throat or wound isolates; $P < 0.05$.

TABLE 5. Serotypes and biotypes of 27 *C. albicans* isolates from 23 adult nonburn patients

No. (%) of different patients with that serotype and biotype	Serotype and biotype
1 (3.7)	A050, A057, A117, A133, B136, A177, B230, A315, B351, B537, A557, B557, B577, B616, B757, B777
2 (7.4)	A351, A357, B456, B457
3 (11.1)	A333

except for their citrate assimilation test results (Table 6). Significantly more isolates from the pediatric burn patients could assimilate citrate than could isolates from the adult nonburn patient population.

DISCUSSION

A total of 64 different serotype-biotype number combinations were found among the 96 pediatric burn patients (Table 3), and 19 were found among the 23 adult nonburn patients (Table 5). For both the pediatric burn and the adult patients, serotype B correlated with flucytosine resistance (a score of 4 or more in the first set of biotype tests). These findings are in agreement with those of a study of *C. albicans* phenotypes in which a more general patient population was used (14). Comparison of the nine individual biotyping test results for isolates from these two patient populations showed a remarkable similarity in the percentage of isolates with any one characteristic (Table 6). For one of the tests, however, the results were significantly different. A total of 98% of the isolates from the burn patients assimilated citrate, while significantly fewer (74%) isolates from the adult nonburned group grew on this carbon source. While these results only apply to the 128 pediatric burn isolates studied, two studies by Odds and Abbott (12, 13) showed that 70% of 92 isolates (12) and 76% of 50 isolates (13) from mixed patient populations assimilated citrate. Hence, although the adult nonburn population in this study was small, the results for citrate assimilation in this group agreed well with those of studies of citrate metabolism by isolates from other patient populations. Why more of the *C. albicans* from the burn patients could utilize citrate as their sole carbon source is not known; however, an investigation of this phenomenon might provide some clues to *Candida* pathogenesis in burn patients.

Nearly 30% of the pediatric burn patient isolates had the same partial biotype, -57. The finding that this partial biotype

TABLE 6. Percentage of individual biotype characteristics in *C. albicans* isolates from two patient populations

Characteristic	% Biotype characteristics in isolates from:	
	Adult nonburn patients (n = 27)	Pediatric burn patients (n = 126)
pH 1.4 tolerance	70	75
Proteinase production	48	38
Flucytosine resistance	41	34
Urea assimilation	100	99
Sorbose assimilation	37	33
Salt tolerance	63	65
Citrate assimilation[a]	74	98
Boric acid resistance	78	83
Safranine resistance	67	69

[a] Significantly more isolates from the pediatric burn patients than from the adult nonburn patients assimilated citrate; $P < 0.01$.

was present to a similar extent (30%) in the adult nonburn patients suggests that strains with the -57 test results have no particular survival advantage in or affinity for pediatric burn patients, but that perhaps this partial biotype is present at this high frequency in a number of patient populations. This possibility is supported by reports of a systemic *C. albicans* biotype -55/7 outbreak in an intensive care unit (3) and by findings of *C. albicans* biotype 153/7 in 60% of 43 heroin addicts (8). It is possible that isolates that express this phenotype are actually more virulent than other *C. albicans* strains, since in a study of vaginal yeast isolates, the -57 partial biotype was more commonly associated with high clinical scores, which were determined by both the subjective symptomatology by the patient and by the clinical impression of genital pathology by the attending physician (15).

In the majority of the burn patients with the -57 test result, strains were specifically serotype B, biotype 557. They therefore differed in serotype from the -57 strains studied previously (3, 8). Isolates with this biotype grew in all three resistance tests and were resistant to all substances tested in the biotyping series. One might speculate that such resistance properties could cause these strains to be more virulent, or at least to persist longer, and therefore be found more frequently. One result of the resistance testing which was unexpected, however, was the finding of a higher percentage of stool versus throat or wound isolates which were resistant to safranine (Table 4). Why more isolates from this site could survive in the presence of this dye is unclear, but it may be worth investigating, especially since the gastrointestinal tract has been implicated as a primary portal of entry for systemic candidiases (24).

The finding of 20 of 96 patients (Table 3) in a single hospital over a 3-year period who were colonized or infected by a *C. albicans* strain with the same serotype and biotype raises the question of in-house transmission. Of the 20 patients with biotype 557 isolates, 11 had the fungus on admission; 9 patients were considered to have acquired the isolate while in the hospital. It is possible that some of the acquired isolates could have been present on admission but were simply not detected, since cultures were not taken from all sites on admission. In addition, to be termed acquired a previously uncultured isolate only needs to be found 5 days postadmission. From the data available (admission dates, hospital bed locations, and isolation dates), transmission in-house did seem probable in one case. In this case, one patient, after sharing a room with another patient who had a documented serotype B, biotype 557 infection, subsequently developed a *C. albicans* serotype B, biotype 557 infection. Since much of this study was done retrospectively with frozen isolates, it was not feasible to go back to obtain environmental and personnel samples to better define possible transmission vectors. Use of this system either routinely or in suspected cases of *C. albicans* epidemics, however, could, and in one instance did (2, 3), aid in solving transmission problems.

In 87% of the pediatric burn patients, only a single *Candida* species (99 of 113 patients; Table 1) or a single strain within the species (28 of 31 patients with multiple *C. albicans* isolates) was isolated. Hence, once isolated the same *Candida* species persisted over time, as exemplified by patients F and D (Table 2). A possible exception to this generalization is patient G (Table 2), who in May 1985 had *C. albicans* serotype A, biotype 15/77, but in November 1986 had *C. albicans* serotype A, biotype 1/233. Depending on which biotypes are compared, these two groups of *C. albicans* isolates differed by two or three biotyping tests. To allow for variations in test results (12), we required three or more biotyping tests to be different before two isolates were considered to be different *C. albicans* strains. Hence, because only two tests were different, as in biotype 157 versus biotype 133, it is suggested that the initial treatment for this patient was not completely successful and that the same *C. albicans* resurfaced later. Differences in the results of three tests, as in biotype 157 versus biotype 233, suggest that the first infection was successfully treated and that the second episode represented colonization by a new *Candida* species. The difference between the initial versus the later biotyping test results in patient G could also be attributed to phenotypic switching, as described by Soll and colleagues (20, 22). If this were a case of phenotypic switching, then the same *Candida* strain would essentially be present, but would just express itself differently at the two different times. For cases such as that of patient G, more information, such as work with genetic probes, is needed.

A low percentage of the burn patients (13%) were colonized by more than one species of *Candida* (14 of 113 patients; Table 1) or by more than one strain of the same *Candida* species (3 of 31 patients from whom multiple *C. albicans* cultures were taken). The finding that a patient can be colonized or infected by more than one strain of an organism is not new. By using the system of Odds and Abbott (12), O'Connor and Sobel (10) found that 20% of 35 rectal *C. albicans* isolates were different from vaginal isolates in the same patients. Warnock et al. (26), using a resistogram system of typing, reported that 14 of 30 patients had different oral than vaginal *C. albicans*. Different strains of bacteria, for example, *Pseudomonas aeruginosa*, have been found to occur simultaneously in hospitalized patients, in general (19), and in cystic fibrosis (25) and burn (7) patients, in particular. The occurrence of cocolonization may explain treatment failures, especially when single antimicrobial agents are used. For example, patient B (Table 2) had *C. albicans* stool colonization with *C. albicans* biotypes 104 and 557. Since most isolates of susceptible yeasts are inhibited by 8 μg or less of flucytosine per ml and are killed by 16 μg or less per ml (18), treatment of this patient with flucytosine might eliminate *C. albicans* biotype 104, which the biotype screening with 25 μg of flucytosine per ml suggests is susceptible to this common antifungal agent. However, this treatment would not eliminate the biotype 557 strain, which, from results of the biotyping test, was found to be resistant to this agent. Hence, treatment of this patient with this antifungal agent would not be successful, because at best only one of the *C. albicans* would be affected. As more antifungal agents become available, the ability of the laboratory to define the number and characteristics of the infecting fungi may become more important in helping the clinician to choose the best agent or combination of agents to successfully treat all *Candida* infections in any one patient.

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