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## Oral *Candida* infection and colonization in solid organ transplant recipients

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### Abstract

**Introduction**—Oral *Candida* carriage and infection have been reported to be associated with a greater risk for systemic infection in transplant recipients; however, a systematic analysis of the oral *Candida* titers and species has not been previously conducted. The objectives of this study were to determine the prevalence of oropharyngeal candidiasis, the oral carrier status, *Candida* titers and species in this population.

**Methods**—Ninety kidney and heart transplant subjects and 72 age-matched healthy controls were included. Swabs from the oral mucosa and a standardized amount of unstimulated saliva were plated on Chromagar™ *Candida*, and colony-forming units per millilitre were calculated. Initial speciation was based on colony color and was confirmed by standard germ tube, biotyping, or polymerase chain reaction assays.

**Results**—Infection with *C. albicans* was detected in seven transplant subjects and none of the controls. The transplant group had significantly higher oral *Candida* titers than the control group. There were no statistically significant relationships between the dose or type of immunosuppressants and oral *Candida* titers or infection. A significantly higher percentage of transplant subjects were colonized by more than one species, compared with control subjects. The most frequent species combination in transplant subjects was *C. albicans* and *C. glabrata*. *C. glabrata* was isolated from 13.5% of transplant carriers and none of the controls.

**Conclusions**—Increased oral *Candida* infection and carriage titers were found in the transplant population. Although the majority of transplant patients were colonized by *C. albicans*, *C. glabrata* appears to emerge as the second most prevalent species.

### Keywords

*Candida albicans*; *Candida glabrata*; transplant; oral candidiasis

Oropharyngeal candidiasis (OPC) is an opportunistic infection caused by *Candida*, a ubiquitous fungal organism that is part of the normal microbiota of the oropharyngeal and

gastrointestinal tract. OPC is a major cause of morbidity in immunocompromised patients (7) and can predispose these patients to esophageal candidiasis (19,46), an invasive form of infection with significant morbidity and higher risk for fatal, disseminated infection (42,44). *Candida albicans* is the species implicated in the overwhelming majority of OPC cases in immunocompromised patients (7,12), although other species such as *Candida glabrata* are recently emerging as possible etiological agents (8,11).

Invasive fungal infections attributed to *Candida* species are particularly prevalent after organ transplantation, especially in the immediate post-transplant period (30). *Candida* can trigger bloodstream, esophageal, gastrointestinal, respiratory and urinary tract infections in solid organ transplant recipients, with prevalence during the first 6 months after transplantation ranging between 5 and 50% depending on the type of transplant (e.g. renal vs. liver) (4,19, 29). It was reported that up to 80% of *Candida*-esophagitis episodes in renal transplant patients were preceded by oral thrush or colonization (4,19). In addition transplant patients with OPC, who are otherwise asymptomatic, are frequently discovered to have esophageal candidiasis upon endoscopy (21).

Despite the increased prevalence of other fungal infections in solid organ transplant recipients, the overall significant morbidity of OPC, and its possible implications in more invasive esophageal infections, few studies have assessed the prevalence of OPC in this population and all of these were conducted outside the USA (3,12,18). In addition, the oral carriage frequency, intensity of carriage, and speciation of *Candida* colonizing transplant patients who are clinically stable, and consequently unlikely to present transient fluctuations in the oral microbial flora due to changes in the immunosuppressive regimen, have never been studied before. In this work we studied the prevalence of OPC, *Candida* carriage frequency, titers and species colonizing the oral mucosa, in clinically stable transplant patients who were at least 1 year post-transplant, and examined relevant risk factors.

## Materials and methods

### Subject selection criteria

One hundred and forty-four consecutive kidney and cardiac transplant patients were screened during routine, outpatient, follow-up visits at the transplant unit in Hartford Hospital, between March 2005 and 2006. We chose kidney and heart transplant recipients because these are the most commonly transplanted solid organs (Scientific registry of transplant recipients, <http://www.ustransplant.org>). Of these patients, 90 were included who met the following criteria: (i) at least 1 year post-transplant, (ii) no history of antibiotic, antifungal, or antiviral usage during the previous 4 months. All transplant subjects were clinically stable, which was defined as having stable serum creatinine levels compared with baseline (kidney only) and no signs of recurrent primary disease, or acute rejection (both organs). These patients were invited to enter the study after clearance by the physician following each case.

Control subjects included 72 age-matched individuals, recruited through an e-mail broadcast to University of Connecticut Health Center employees (36 subjects), local General Clinical Research Center and Women's Health Center mailing lists (16 subjects), or advertisements in local area newspapers (20 subjects), during the same time period. These subjects had no immunological compromising condition and had no history of antibiotic, antifungal, or antiviral use during the previous 4 months. After an explanation of the study, the overall risk-benefit analysis and final determination of eligibility, written informed consent was sought from each of the participants. Following the guidelines of the local Institutional Review Board, subjects were notified of their right to refuse to participate or to withdraw at any time, without affecting their medical or dental care.

## Data collection

The medical records of the transplant subjects were reviewed and all relevant information was collected using a standardized data extraction form. Information included subject demographics, medical history including history of fungal infections and antifungal medications, graft failure risk factors, history of acute or chronic graft rejection, and current medications.

## Oral examination and microbial sampling

A complete oral examination was performed in all subjects. Oral colonization (healthy carrier state) was considered in asymptomatic, lesion-free subjects, with *Candida*-positive saliva or dorsal tongue swab cultures. Infection was defined as clinically suspicious lesions (erythematous, hyperplastic, or pseudomembranous) and testing positive by culture on BBL CHROMagar™ *Candida* medium (Becton Dickinson, Rockville, MD). The number of colony-forming units (CFU) of *Candida* present in a standardized amount of unstimulated saliva (3 ml) was counted after plating samples on CHROMagar™ *Candida* medium and the CFU/ml of saliva was used as an indicator of *Candida* titer/load in each subject. Subjects were asked not to drink or eat for at least 1 h before saliva collection. Sterile oral swabs were additionally used to sample the dorsal surface of the tongue in all subjects, or the surface of clinically suspicious mucosal lesions in subjects with such lesions. Swab samples were plated directly on CHROMagar *Candida* medium and were used to complement species analyses. Colony number and color were assessed at 35°C for up to 5 days. Subjects with high *Candida* titers were considered those with >1000 CFU/ml detected in unstimulated saliva (15,25). Colonies were initially speciated by their characteristic color on CHROMagar *Candida* plates and confirmed by a germ tube test at 37°C, and standard sugar assimilation assay profiles (RapID Yeast Plus System, Lenexa, KS). The vast majority of isolates were conclusively identified on the basis of the results of the RapID yeast identification system. Polymerase chain reaction was required to identify four of the *C. glabrata* isolates, which did not give conclusive sugar assimilation assay profiles. This selective polymerase chain reaction strategy for *Candida* speciation has been published by others in similar oral carriage epidemiological studies (23).

## Statistical analyses

A logistic regression was run on the dichotomous dependent variables (*Candida* presence/absence in saliva or tongue mucosa, and high/low *Candida* loads in saliva), as a function of the three-level predictor variable, i.e. transplant status (kidney, heart, or no transplant). *A priori* contrasts were used that provided two orthogonal tests: either kidney vs. no transplant and heart vs. no transplant, or transplant vs. no transplant and kidney vs. heart. The results in these analyses are given as odds ratios (OR) together with 95% confidence intervals (95% CI). When a frequency of zero occurred within any of the three groups (kidney, heart, or no transplant), the Fisher's exact test was used to calculate significance levels. For continuous dependent measures (e.g. *Candida* in CFU/ml) a *t*-test or analysis of variance (for multiple group comparisons) was used to test whether groups had significantly different levels of the measure. Bivariate associations between continuous or dichotomous independent measures were run using the Pearson correlation test or the Yates-corrected chi-square test, respectively. Variables that were skewed were logarithmically transformed. Two-tailed tests were routinely used, and values in parentheses of respective tests indicate the degrees of freedom.

## Results

### Population characteristics

There were significantly more diabetics and former smokers in the transplant group compared with the control group (Table 1). There were only two current smokers in the transplant group.

Two transplant subjects had a history of intra-oral (tongue) or peri-oral squamous cell carcinoma (lip), whereas three additional transplant subjects had a history of squamous or basal cell carcinoma of the skin in the neck and head regions. None of the controls had a history of head and neck neoplasia. This finding is consistent with the greater overall risk of transplant patients for developing skin or mucosal carcinomas (13,24).

Overall, 23% of kidney and 33% of heart transplant recipients and none of the controls had a positive history of receiving oral antifungal treatment (Table 2). In the transplant group there was a significant association between the presence of diabetes and history of antifungal treatment (28% of the diabetics in the transplant group had a positive history of antifungal use, compared to 10.3% of non-diabetics), such that those who had diabetes were more likely to have received antifungals post-transplant, ( $\chi^2_{(1)}=4.28$ ,  $P = 0.039$ , 2-t). Subjects who had received antifungals were also on higher doses of prednisone, than those who did not receive oral antifungals ( $t_{(87)} = 2.54$ ,  $P = 0.013$ ). In contrast, none of the transplant subjects on cyclosporine A treatment had a positive history of antifungal use, compared with 27.4% of those not on cyclosporine A who had been treated with antifungals. This resulted in a significant negative association between cyclosporine A and history of antifungal treatment ( $\chi^2_{(1)}=8.84$ ,  $P = 0.003$ , 2-t).

### Oral clinical and microbiological findings

There was no significant difference in the average number of missing teeth between the two groups or in the frequency of removable oral prostheses. The prevalence of self-reported xerostomia did not differ between the transplant and control groups ( $P = 0.4$ ). Among the 90 transplant recipients, only seven (six kidney and one heart transplant subject) showed clinical and microbiological evidence of erythematous candidiasis on the dorsum of the tongue or hard palate, occasionally accompanied by a mild burning sensation. *C. albicans* was the species isolated from all these lesions. None of the controls had oral candidiasis, resulting in a significant difference from transplant subjects ( $P = 0.004$ ).

The frequency of asymptomatic colonization in transplant recipients (57.7%) was not significantly higher, compared with healthy controls (50%). In addition, logistic regression showed that the type of transplant (heart vs. kidney) did not significantly affect the frequency of colonization (Wald = 0.08,  $P = 0.78$ , OR 1.22, CI 0.31, 4.87). When all groups were considered, there was no relationship between the presence of diabetes and *Candida* colonization in the oral cavity ( $P = 0.57$ ), or between the presence of diabetes and high (>1000 CFU/ml) vs. low (<1000 CFU/ml), oral *Candida* titers ( $P = 0.4$  for all species,  $P = 0.19$  for *C. albicans*). Age ( $r_{(160)} = 0.11$ ,  $P = 0.15$ ), and gender ( $t_{(159)} = 1.71$ ,  $P = 0.09$ ), also did not significantly influence the total *Candida* titers in saliva.

The mean CFU/ml titers for all species were significantly higher in transplant subjects (mean log CFU/ml = 18.4) compared with controls (mean log CFU/ml = 2.01,  $t_{(160)} = 2.03$ ,  $P = 0.04$ ), whereas comparison of the mean log-transformed CFU/ml for *C. albicans* only, showed a trend for significance between the two groups (mean log CFU/ml for controls = 5.3, mean log CFU/ml for transplant 12.2,  $t_{(160)} = 1.66$ ,  $P = 0.09$ ). When oral titers were compared between kidney and heart transplant subjects, there were no statistically significant differences in the mean log CFU/ml titers for all species ( $t_{(88)} = 0.33$ ,  $P = 0.9$ ) or for *C. albicans* ( $t_{(88)} = 0.56$ ,  $P = 0.5$ ). Surprisingly, there was no statistically significant relationship between the presence of diabetes, type or dose of individual immunosuppressants, the presence of triple pharmacological immunosuppression, or the duration of immunosuppression, with oral *Candida* titers or infection.

The frequency of *C. albicans* isolation in transplant and control carriers was similar (approximately 80%, Fig. 1). However, the frequency of *C. glabrata* colonization was higher in the transplant group [8.6% of all transplant subjects ( $n = 90$ ), or 13.5% of transplant *Candida* carriers ( $n = 52$ )], as compared with controls (0% or 0/72 healthy subjects,  $\chi^2_{(1)}=5.85$ ,  $P = 0.016$ , 2-t, for subject-based comparisons). No other significant differences in the types of species isolated were noted between transplant and control carriers (Fig. 1), or between kidney and heart transplant subjects (Table 3). Seventeen of the 90 (18.9%) transplant subjects (or 32.6% of the transplant *Candida* carriers) harbored multiple species in the oral cavity compared with three of 72 (4.2%) healthy subjects (or 8.3% of healthy *Candida* carriers,  $n = 36$ ), a difference which was statistically significant ( $\chi^2_{(1)}=4.00$ ,  $P = 0.045$ , 2-t, for subject-based comparisons). The most frequent species combination in transplant subjects was *C. albicans* and *C. glabrata*.

## Discussion

In this study we found a greater prevalence of OPC in subjects with functional renal or cardiac transplants later than 1 year post-transplant, compared with control subjects. Higher OPC prevalence has been previously reported in renal and liver transplant patients, but these reports included smaller or poorly characterized populations, and did not focus on patients who were clinically stable and at least 1 year post-transplant. Moreover, none of these previous studies included US populations (3,6,9,14,18,39). Our findings suggest that the prevalence of this oral infection in solid organ transplant recipients in the US (7.7% according to our study) may be lower compared with other areas in the world, such as the Middle East or eastern Europe, where reported prevalence rates range between 15 and 64% (3,14,18). Such differences may be attributable to variations in population characteristics among studies, including time after transplantation, immunosuppressant regimens or overall health status of the transplant populations examined. The OPC detected in our population was exclusively of the erythematous type and was fairly localized, which is consistent with other reports of OPC in renal transplant patients (3).

Immunosuppressant medications commonly taken by transplant recipients, such as corticosteroids, adversely affect all aspects of immunity (26) and certain antiproliferative medications, such as mycophenolate and azathioprine, can trigger neutropenia, which is one of the most important predisposing factors to candidiasis (7). The finding that phagocyte anti-fungal responses are significantly impaired in transplant recipients (32) may also help to explain their increased susceptibility to oroesophageal infection. Although immunosuppressants seemingly elevate the risk for OPC, significant associations between dosages and higher risk for infection were not demonstrated in this or other studies (3), possibly because of the requirement of pharmacologically homogeneous or larger transplant populations for statistically significant results.

Increased rates of asymptomatic oral colonization with *Candida* are common in immunosuppressed patients (22,27,45). However, the oral *Candida* colonization rate in this US transplant population (57.7%) was not significantly different from that in controls and was lower than that reported in transplant populations in other countries (75–80%) (3,14). For reasons that are not entirely understood, geographic location is one of the determinant factors of both incidence of *Candida* infection and species distribution in population surveillance studies (10,20,31). This may help to explain the disparities between our findings and the findings reported from other parts of the world.

Despite the reported differences in the epidemiology of fungal infections among different transplanted organs (30), we were not able to demonstrate significant differences in oral



*Candida* colonization frequency, or titers between kidney and heart transplant subjects. This may be related to the fact that our heart transplant group is small, and consequently underpowered, for meaningful statistical comparisons. In addition, there were no differences in the clinical characteristics or immunosuppressive regimens between the two groups, which may explain the lack of significant differences in the oral microbiota. However, it should also be noted that the differences in the epidemiology of fungal infections among different organ transplants pertain mostly to the early post-transplant period and are related to environmental exposure of the transplanted organs (30).

Although oral colonization is one of the most frequently identified risk factors of OPC (16, 17,28,41), the clinical significance of the increased *Candida* titers in the oral cavity of transplant patients is unknown. A recent study in transplant patients showed that the vast majority of patients who developed invasive fungal infections were orally colonized with *C. albicans* and there was also a significant correlation between oral colonization and the subsequent development of invasive respiratory or gastrointestinal infection (4). Therefore, the increased oral fungal burden in this population may play a potentially important role in the subsequent development of infection. Although prophylactic antifungals have been shown to reduce intestinal colonization, they appear to be ineffective in lowering the incidence of oral mucosal infection or colonization in bone marrow transplant patients (1,9,38,43). Therefore the routine prophylactic use of antifungals in transplant patients with high levels of oral *Candida* colonization is probably inappropriate, unless oral infection is present.

Although *C. albicans* was the primary oral *Candida* species isolate in this and other studies of immunocompromised patients (22,45), *C. glabrata* is isolated with increasing frequency in these patients (2,40). Previously, *C. glabrata* was considered a relatively non-pathogenic saprophyte of the normal flora of healthy individuals (8,11). In recent studies *C. glabrata* has emerged as a notable pathogenic agent in OPC in patients receiving radiotherapy (5,33-36). In fact, the failure of prophylactic antifungals in lowering the incidence of infection in immunocompromised patients has been partly attributed to the positive selective pressure of azoles on *C. glabrata*, which is naturally resistant, and the potential active role of this organism in infection (43). Although longitudinal studies are needed to determine the role of the increased oral *C. glabrata* carriage in the subsequent development of infection in transplant subjects, it has been reported that cancer patients who carried this yeast in saliva, throat, and rectum had the highest percentage of subsequent infection (2).

Mixed species of *Candida* were identified in a higher percentage of the transplant patients than in the control subjects in this study, a report that is in agreement with a previous study in a human immunodeficiency virus (HIV) -positive population (45). This finding may be indicative of the possibility that several species, which are normally more vulnerable to host immunity, are allowed to thrive under this immunosuppressed, more permissive host environment. The clinical significance of the presence of mixed *Candida* species in the oral cavity is not entirely understood. However, oral infections with mixed *Candida* species have been reported to be more persistent, and more difficult to treat (37). In addition, more severe symptoms have been noted in HIV-infected and cancer patients with mixed *C. albicans* and *C. glabrata* oral infections (33-35).

In conclusion, this study has shown an increased prevalence of oral infection and higher oral *Candida* titers in stable renal and cardiac transplant subjects, compared with healthy controls. The emergence of *C. glabrata* as a colonizer of the oral cavity in this population and the presence of multiple *Candida* species are also important novel findings in this study. Future longitudinal studies should explore the role of increased *Candida* carriage burden in the development of symptomatic oral or esophageal infection in this population.

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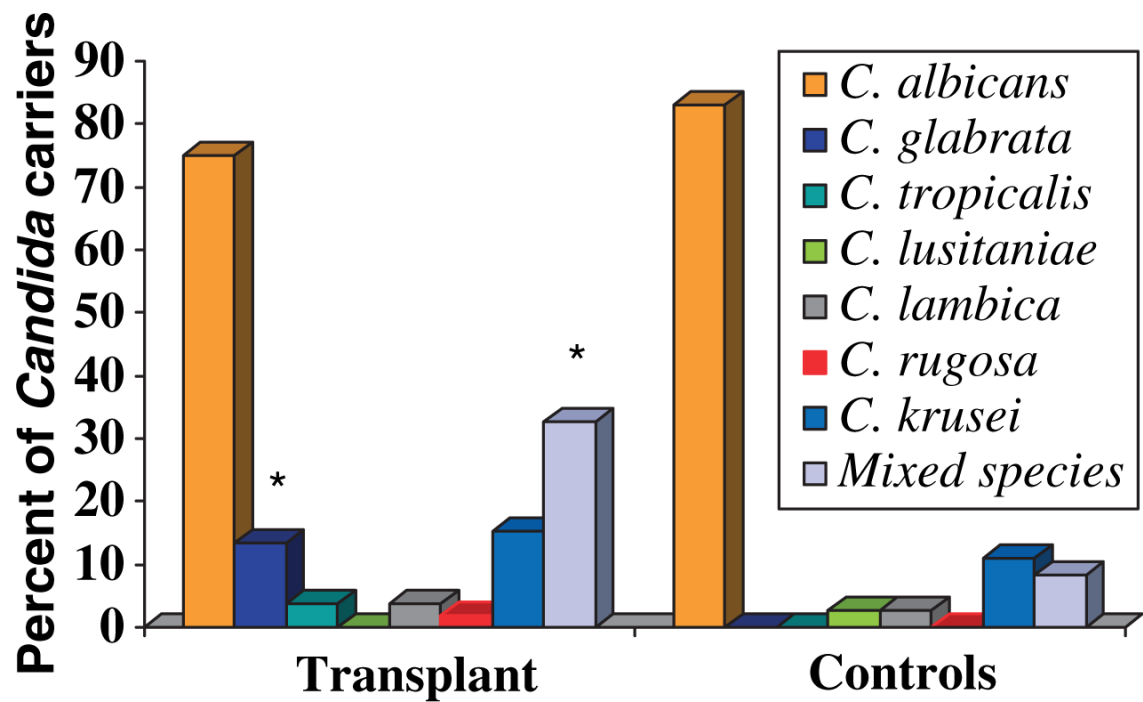
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**Fig. 1.**

Frequency of *Candida* species isolated from the oral cavity of transplant and control *Candida* carriers. \* $P < 0.05$  compared to controls.

**Table 1**

Summary of subject demographics

Variable	Kidney ( <i>n</i> = 81)	Heart ( <i>n</i> = 9)	Control subjects ( <i>n</i> = 72)	<i>P</i> value, transplant vs. controls
Age (years)	52.7 ± 11.9	56.4 ± 12.3	53 ± 10	0.329
Gender (female) (%)	42%	44%	60%	0.03
Diabetics (%)	54%	67%	3%	<0.0001
Smokers (former) (%)	41%	75%	0%	<0.0001
Smokers (current)	0%	22%	0%	0.12
Removable dental prostheses	3.7%	0%	0%	0.11
Number of missing teeth	4 ± 4.6	6.11 ± 6.8	1.69 ± 2.1	0.06

Mean values and SD are shown for continuous variables and frequency values (%) are shown for dichotomous variables.

**Table 2**

## Characteristics of transplant population

Clinical characteristics	Kidney ( <i>n</i> = 81)	Heart ( <i>n</i> = 9)	<i>P</i> value, kidney vs. heart
Post-transplant years (mean)	6.8 ± 4.8	8.1 ± 5.3	0.57
Rejection history	35%	44%	0.58
History of antifungals	23%	33%	0.50
Cyclosporin	31%	33%	0.88
Prednisone	93%	89%	0.70
Mycophenolate	74%	89%	0.33
Tacrolimus	63%	56%	0.67
Azathioprine	19%	11%	0.58
Sirolimus	11%	11%	1.00

Mean values and SD are shown for number of years since transplant surgery, and frequency values (%) are shown for dichotomous variables.

**Table 3**Frequency of *Candida* species isolation in each organ transplant type

<i>Candida</i> species	Kidney (n = 81)	Heart (n = 9)	P value, kidney vs. heart
<i>C. albicans</i>	44%	44%	1.0
<i>C. glabrata</i>	8.6%	0%	0.36
<i>C. lambica</i>	2.4%	11.1%	0.17
<i>C. rugosa</i>	2.4%	0%	0.63
<i>C. krusei</i>	9.8%	0%	0.32
<i>C. tropicalis</i>	2.4%	0%	0.63
>1 species	19.7%	11.1%	0.53