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# Microbiology and Epidemiology of Oral Yeast Colonization in Hemopoietic Progenitor Cell Transplant Recipients

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## Abstract

**Objective—**We monitored the epidemiology and microbiology of oral yeast colonization in patients undergoing hemopoietic progenitor cell transplantation (HPCT) to examine associations between yeast colonization and oral mucositis.

**Study Design—**One hundred twenty-one consecutive HPCT patients were sampled for oral yeasts prior to fluconazole (FLC) prophylaxis, at transplant, and weekly until discharge. Clinical oral mucositis screenings were performed tri-weekly.

**Results—**Yeast colonization was evident at 216 of 510 total visits. *Candida albicans* and *C. glabrata* were the predominate organisms. Eight patients showed elevated MICs to FLC. One patient developed fungal septicemia. Patients with OMAS mucositis scores <20 had higher colonization rates than those with higher scores.

**Conclusions—**FLC is very effective in controlling a variety of oral yeasts in HPCT recipients. FLC resistant yeasts do emerge and can be the source of fungal sepsis. A positive association was not shown between yeast colonization and presence or severity of oral mucositis.



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**CONFLICT OF INTEREST**

TFP: Research Support/Consultant: Astellas Pharma US, Merck & Co., Viamet Pharmaceuticals, Inc., Toyama Chemical Company, and Pfizer Inc. SWR: Research Support: Pfizer Inc., Merck & Co., Astellas Pharma US Inc. NPW: Research Support/Consultant: Astellas Pharma US, Merck & Co., CyDex, Viamet Pharmaceuticals, Inc., Toyama Chemical Company, and Pfizer Inc. SDW, WRK, JJT, COF: None to declare.

## INTRODUCTION

High-dose chemotherapy with hematopoietic progenitor cell transplantation (HPCT) is an established therapy for patients with hematologic malignancies and selected solid tumors [1]. Oral mucositis and fungal infections remain major complications of HPCT [2, 3]. Routine antifungal prophylaxis with fluconazole (FLC) in HPCT has greatly decreased the incidence of serious *Candida albicans* infections [4–6]. However, other *Candida* species resistant to fluconazole, including *C. glabrata* and *C. krusei*, have emerged [3, 4]. We have previously reported that oral colonization with *C. glabrata* [7] or *C. krusei* [8] can lead to fungal sepsis in hemopoietic progenitor cell recipients. In the era of FLC prophylaxis, there is limited information regarding the oral fungal colonization of transplant recipients before and throughout the transplant course.

We performed a prospective longitudinal surveillance study of HPCT recipients using oral sampling to evaluate the prevalence of oral yeast microbiology before transplantation and the epidemiology of yeast resistance before and during the HPCT process. The study cohort was also evaluated for levels of oral mucositis since this is a common side effect of HPCT conditioning regimens [9–11]. Severe mucositis can cause painful dysphagia, limiting the patient's ability to maintain a normal diet or take oral medications. This debilitating complication can increase the need for opioid analgesics, prolong inpatient stays and increase costs [12, 13]. Ulcerative mucositis compromises oral mucosal integrity and can increase risk of bacteremia or fungemia due to systemic invasion of endogenous flora [10, 14]. Our purpose was to determine the change in oral yeast colonization in patients undergoing HPCT who received fluconazole prophylaxis. Additionally, we sought to determine whether there was any association between oral *Candida* colonization and presence of oral mucositis.

## MATERIALS and METHODS

### Patient population

We conducted a longitudinal, prospective study of 121 consecutive HPCT recipients with hematologic malignancies who underwent high dose chemotherapy (Table 1) followed by transplantation from July 2005 through February 2008. Our patients were referred to the South Texas Veterans Health Care System, Audie L. Murphy Division, San Antonio Texas Bone Marrow Transplant Unit from 28 different referring centers throughout the nation and Commonwealth of Puerto Rico. Each patient received antifungal prophylaxis with oral fluconazole 400 mg daily starting with conditioning regimen and continuing through engraftment. As inpatients, compliance was assured by the daily nursing staff administration and documentation of all medicinal regimens. If the patient was unable to tolerate p.o. medications intravenous routes were utilized. Informed consent was obtained from all participants/patients, and all procedures were in accordance with the Institutional Review Board of the University of Texas Health Science Center at San Antonio (UTHSCSA) and the Research and Development Committee of the South Texas Veterans Health Care System.

**Oral Rinse Sample Collection and Microbiological Characterization, Mucositis assessment—**Sampling consisted of a 20 second oral swish with 10 ml of sterile water. On three occasions, an oral swab culture was substituted since oropharyngeal candidiasis (OPC) was evident or the patient was unable to swish and expectorate. Samples were taken before the initiation of the conditioning regimen and fluconazole prophylaxis (visit 1), the day of transplant (visit 2) which was 5.5±2.59 days later with weekly sampling until discharge (visits 3 and 4) 12.02±2.77 and 19.04 ±3.38 days later respectfully.

Samples were plated on CHROMagar *Candida* (DRG International, Mountainside, NJ) media containing chloramphenicol (0.5g/L) with fluconazole (8 and 16 μg/mL) or without fluconazole for presumptive fungal identification and resistance screening [15]. These chromogenic medium plates were prepared in 100-mm-diameter petri dishes and stored at 4°C for up to one week prior to use. CHROMagar *Candida*-specific color patterns were used for presumptive yeast identification. Yeasts were further characterized using germ tube analysis after incubation in human serum at 37°C for 3 h, and by biochemical utilization patterns determined using API 20C (bioMérieux, Marcy-l'Etoile, France). Tri-weekly oral examinations utilizing both the World Health Organization (WHO) [12, 14] and the Oral Mucositis Assessment Scale (OMAS) [16] criteria were utilized for mucositis assessment and were performed by the same two healthcare providers (SDW and JJT). All patients participated in periodic oral fungal surveillance.

**Antifungal Susceptibility—**Minimal inhibitory concentrations (MICs) of these yeasts were determined using the Clinical and Laboratory Standards Institute (CLSI) methodology [17] by the Fungus Testing Laboratory at UTHSCSA. Yeast isolates with fluconazole MICs of ≥16 μg/mL were considered to be resistant in this study [18].

## RESULTS

Our study population was 94% (112 of 119) male with a median age of 58 years (range 19 to 74, mean 55.4±11.5 years). Fifty-three percent (63 of 119) were white, 25 % (30 of 119) hispanic, 20% (24 of 119) black, and 2% (2 of 119) other races. Patients enrolled in this cohort received 106 autologous, 11 allogeneic and 2 syngeneic transplants. Two patients died prior to transplantation.

A variety of yeasts were cultured from the HPCT patients enrolled in this study. Yeast colonization was evident in 216 of the 510 total visits (42%; Table 2). Nine different yeast species were cultured from samples taken at these visits. *Candida albicans* and *Candida glabrata* were the predominate organisms in the cultures, and most specimens were susceptible to fluconazole, as shown in Table 2.

Three patients with OPC and five other patients who were only colonized with yeasts showed elevated MICs to FLC. In our patient population, fluconazole resistance, defined as MIC ≥16 μg/mL, was seen in *C. glabrata, C. krusei, C. dubliniensis* and *C. tropicalis,* as shown in Table 3 In each of these patients the fluconazole. MICs increased over time (data not shown) with the exception of patient 34, in whom the *C. glabrata* isolate rapidly regained susceptibility once prophylaxis with FLC was discontinued and echinocandin therapy was initiated [19].

Colonization by single species was common throughout the duration of the study with *C. albicans* and *C. glabrata* being the predominating organisms. However, the rate of colonization by multiple organisms was relatively low, being noted in only 27 of 216 (13%) total colonized visits. *Candida glabrata* was present in 25 of 27 (93%) of the visits where multiple colonization was noted. In addition, *C. glabrata* was present in 6 of 8 (75%) of patients colonized with multiple organisms, while *C. krusei*, *C. dubliniensis* and *C. tropicalis* were each present in only one patient. Patient 34 was colonized concurrently with *C. glabrata* and *C. dubliniensis* in the first visit, *C. glabrata* and *C. tropicalis* on the second visit, and only with *C. glabrata* on subsequent visits. Rates of colonization decreased by visit 4 when engraftment had occurred and antifungal therapy had been discontinued as shown in Figure 1. Interestingly, despite the large number of colonized visits, only three episodes of clinical OPC were seen during the study. OPC manifested as a pseudomembranous form with soft friable, creamy colored plaques on the oral mucosa. One patient had *C. albicans*

OPC on his initial visit, while a second patient (patient 28) developed OPC on his third and fourth visits with *C. krusei.* This patient also developed *Candida* fungemia secondary to oral carriage and has been described in a previous publication [8]. As a result of their pretransplant conditioning regimens (Table 1) most of our patients developed various degrees of oral mucositis starting 5–7 days after their conditioning therapy and continuing through neutrophil engraftment. None of our patients received Total Body Irradiation (TBI) as part of their treatment protocol. Ten of the patients showed no evidence of oral mucositis throughout their course of treatment while 25 had WHO mucositis scores of 3 or above. Interestingly, 21 of our patients who developed significant oral ulcerative mucositis with OMAS scores >20 at a single visit showed lower rates of yeast colonization or infection than those who did not develop significant mucositis. Yeast colonization during one or more of the first four visits was seen in 9 of these 21 (43%) patients with severe mucositis (Table 4). In contrast, those patients with mucositis scores <20 had higher colonization rates (66 of 98; 67%; $p < 0.05$ per Fischer's exact test). WHO mucositis scores showed a similar pattern with patients receiving the highest scores (>3) having the lowest rate of yeast colonization. Interestingly, the WHO and OMAS mucositis grading systems associated very nicely when the categories of pain ($p<0.01$), hospitalization days, and febrile days in this cohort of patients were compared. Both WHO and OMAS scores increased as neutropenia days increased except at a WHO score of 4, and OMAS score of >35 where we noted a slight, nonstatistical decrease (Table 5).

## DISCUSSION

Most institutions utilize antifungal prophylaxis for patients undergoing HPCT [4]. We utilize fluconazole 400 mg p.o. daily from pretransplant conditioning though neutrophil engraftment. Despite this antifungal prophylaxis 45% (53 of 119) of our patients were still colonized at visit 2 (day of transplant). Our patients' conditioning regimen of high dose chemotherapy without TBI in the mainly autologous transplant population resulted in only 18% (21 of 119) of our patients developing significant ulcerative mucositis. In agreement with a similar oral candidiasis study of mainly allogeneic transplant recipients, a positive association was not determined between *Candida* colonization and degree or presence of oral mucositis in our transplant cohort [20]. Our reported lower oral colonization in patients with the highest OMAS and WHO scores may have resulted from less vigorous oral swishing by HPCT recipients as mucositis symptoms increased, which may have captured fewer yeasts. The patients were also encouraged to use an oncology triple mix (lidocaine, kaopectate and diphenhydramine) for symptomatic relief; these additional rinses may have lowered our yeast counts. During the course of this study, both WHO and OMAS mucositis scoring systems were determined and found to have similar utility.

Colonization by *C. albicans* was most prevalent in these patients, however, relatively high numbers of yeasts with a propensity for fluconazole resistance, notably *C. glabrata* and *C. dubliniensis*, were recovered. Also, *C. glabrata* was commonly found in mixed colonization. Despite their presence, most yeast isolates were highly susceptible to fluconazole. In addition, fluconazole prophylaxis appears highly effective as only one patient developed a documented fungemia, and rates of oral yeast colonization deceased by the third visit despite maximum neutropenia at this time. This was especially evident for those with *C. albicans* as the rates of colonization with this species significantly decreased between visit 1 and visit 3 (34% vs. 16%; $p = 0.006$). This is important, as major risk factors for *Candida* fungemia include neutropenia, mucositis and the presence of a central venous catheter, which were present in many of those in this cohort [4]. Fortunately, fungal sepsis with its origin from oral colonization is rare in these patients. However, patient 28 demonstrates that under conditions of severe neutropenia and ulcerative oral mucositis, while receiving fluconazole prophylaxis, oral colonization with *C. krusei* can lead to candidemia with the same

colonizing organism. We compared the third and fourth oral swab cultures of *C. krusei* to subsequent blood and urine isolates using molecular techniques to determine that the initial oral colonization was the likely source of systemic infection. To our knowledge, this was the first report of the relationship documenting *C. krusei* fungemia with oral carriage in an autologous HPCT recipient [8]. We have also previously described, in another population of patients, one other case of *Candida* fungemia from an oral source in an allogeneic HPCT recipient. In this case the offending organism was *C. glabrata* [7]. These two cases, with an oral source, have shown elements common to patients with *Candida* fungemia including severe neutropenia and severe oral mucositis. However they also included colonization with an organism with elevated MICs to fluconazole, such as *C. glabrata* and *C. krusei* [7, 8]. When these organisms are found in oral colonization in HPCT recipients, modification of antifungal prophylaxis should be considered.

## CONCLUSIONS

Measurements for both the WHO and OMAS mucositis grading systems are comparable and closely follow other patient complications such as fever days, hospital inpatient days and pain scores. A positive association was not shown between yeast colonization and the presence or severity of oral mucositis. Fungal organisms that are resistant to FLC can lead to fungal sepsis. When FLC resistant organisms are detected in HPCT recipients, modifications of antifungal prophylaxis should be considered.

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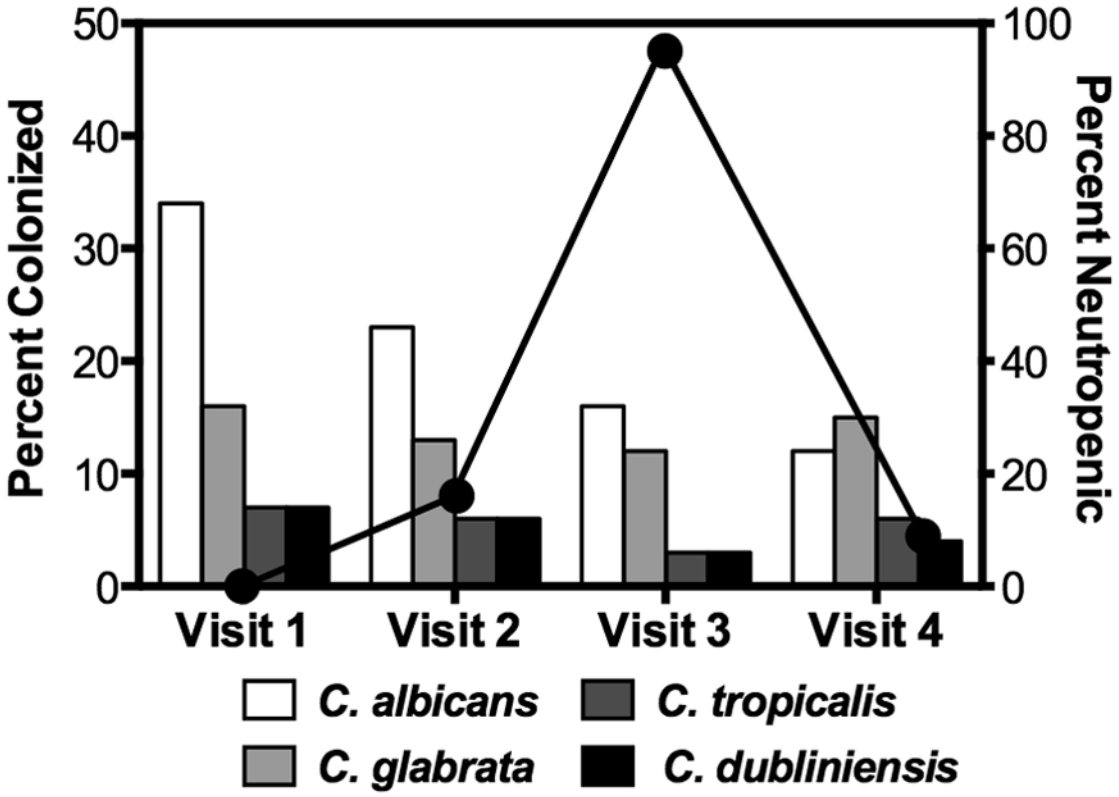


**Figure 1.**
Bar graphs represent the incidence of predominant *Candida* species found in the total patient population for each visit. Percentages do not equal 100% due to mixed cultures. Line graph represents the percentage of patients who were neutropenic (< 1000 cells/mL) at each visit.

**Table 1**

Diagnosis and conditioning regimens

| Diagnosis (Number of patients) | Conditioning Regimen |
|---|---|
| Multiple Myeloma (74) | Melphalan |
| Non-Hodgkins Lymphoma (27) | CBV or BEAM |
| Hodgkin Lymphoma (7) | CBV[1] or BEAM[2] |
| Acute Myelogenous Leukemia (7) | BuCy[3] or BuF[4] |
| Testicular Germ Cell (3) | CEC[6] |
| Chronic Lymphocytic Leukemia (2) | BuF[4] or MelF[5] |
| Myelodysplactic Syndrome (1) | BuCy[3] |

[1] CBV = cyclophosphamide, etoposide, carmustine

[2] BEAM =carmustine, cytarabine, etoposide, melphalan

[3] BuCy = busulfan, cyclophosphamide

[4] BuF = busulfan, fludarabine

[5] MelF = melphalan, fludarabine

[6] CEC = cyclophosphamide, etoposide, carboplatin

**Table 2**

Yeast distribution with fluconazole MIC data in 121 HPCT recipients

| Yeast | Colonized Visits (216) | Total Visits (510) | MIC range (median) |
|---|---|---|---|
| *C. albicans* | 96 (44%) | 96 (19%) | 0.125 – 1.0 (0.125) |
| *C. glabrata* | 76 (35%) | 76 (15%) | 2–64 (4) |
| *C. tropicalis* | 24 (11%) | 24 (4.7%) | 0.125–32 (.25) |
| *C. dubliniensis* | 23 (11%) | 23 (4.5%) | 0.125–32 (0.125) |
| *C. krusei* | 6 (3%) | 6 (1%) | 8–16 (8) |
| *S. cerevisiae* | 5 (2%) | 5 (1%) | 0.5–1 (0.5) |
| *C. parapsilosis* | 4 (2%) | 4 (.8%) | 0.125–0.25 (0.25) |
| *C. magnoliae* | 1 (0%) | 1 (0%) | 0.5 (0.5) |
| *C. lusitaniae* | 1 (0%) | 1 (0%) | 0.5 (0.5) |

**Table 3**

Patients carrying yeasts with decreased fluconazole susceptibility

| Pt # | Yeast | Elevated MIC |
|---|---|---|
| 26 | *C. glabrata* | 16 |
| 28 | *C. krusei* | 16/64 |
| 34 | *C. glabrata* | 32 |
| 34 | *C. dubliniensis* | 32 |
| 34 | *C. tropicalis* | 32 |
| 41 | *C. glabrata* | 32 |
| 50 | *C. glabrata* | 64 |
| 56 | *C. glabrata* | 16 (48hr) |
| 57 | *C. glabrata* | 64 |
| 102 | *C. glabrata* | 32 |

**Table 4**

OMAS mucositis scores >20 and yeast colonization by visit

| ID | Total OMAS | WHO | Yeast V-1 | Yeast V-2 | Yeast V-3 | Yeast V-4 |
|---|---|---|---|---|---|---|
| 7 | 23 | 2 | CA[1] | CA | CA | CA |
| 9 | 22 | 2 | NG[2] | NG | NG | NG |
| 17 | 31 | 3 | NG | NG | NG | NG |
| 22 | 34 | 4 | NG | NG | NG | NG |
| 28 | 32 | 4 | NG | NG | CK[3] | CK |
| 37 | 25 | 2 | NG | NG | NG | NG |
| 44 | 20 | 2 | NG | NG | NG | NG |
| 46 | 32 | 3 | CA | CA | CA | CA |
| 50 | 39 | 4 | CA | CA | NG | NG |
| 51 | 37 | 4 | NG | NG | NG | NG |
| 59 | 27 | 2 | NG | SC[4] | SC | SC |
| 67 | 42 | 3 | CA | CA | CA | CA |
| 69 | 34 | 3 | NG | NG | NG | NG |
| 78 | 35 | 4 | NG | NG | NG | NG |
| 82 | 38 | 4 | NG | NG | NG | NG |
| 90 | 41 | 3 | CT[5]/CG[6] | CT/CG | CT/CG | CT/CG |
| 105 | 25 | 2 | CG | NG | NG | NG |
| 107 | 34 | 3 | CT | CT | CT | CT |
| 112 | 26 | 3 | NG | NG | NG | NG |
| 113 | 37 | 3 | CG | CG | CG | CG |
| 123 | 26 | 3 | NG | NG | NG | NG |

[1] CA: *Candida albicans*

[2] NG: No growth

[3] CK: *Candida krusei*

[4] SC: *Saccharomyces cerevisiae*

[5] CT: *Candida tropicalis*



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$^{6}$CG: *Candida glabrata*

**Table 5**

WHO/OMAS Scores versus therapy sequelae

| WHO | OMAS | Pain* | Diarrhea Days | Fever Days | Hospital Days | Neutropenic Days |
|---|---|---|---|---|---|---|
| 0 | 0.25 | 0 | 7 | 1.66 | 15.8 | 6.91 |
| 1 | 3 | 1.13 | 6.13 | 1.06 | 16.8 | 7.86 |
| 2 | 11.23 | 3.29 | 6.37 | 2.11 | 19.34 | 8.25 |
| 3 | 23.05 | 6.58 | 8.95 | 3.42 | 24.21 | 8.84 |
| 4 | 35.83 | 8.83 | 8.33 | 9 | 53.33 | 7.66 |

P<0.01 vs WHO and OMAS