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Respiratory Tract Colonization by *Candida* species Portends Worse Outcomes in Immunocompromised Patients

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Abstract

Background: The significance and clinical management of *Candida* colonization of the respiratory tract are ill-defined. We now report the frequency of *Candida* species from the lower respiratory tract in hematopoietic stem cell transplant recipients (HSCT) undergoing bronchoscopy with bronchoalveolar lavage (BAL) for pneumonitis post-HSCT.

Methods: The University of Michigan Clinical Microbiology Lab Database was queried for all respiratory cultures positive for *Candida* species between 2000–2012. We concurrently performed a retrospective analysis of 515 HSCT recipients with pneumonitis at our institution between 2001–2012.

Results: During this twelve-year period, there were 2524 unique *Candida* isolates (78% *Candida albicans*). Of the 515 HSCT patients with suspected pneumonitis, 127 (24.7%) HSCT subjects were culture positive for a fungal pathogen, with *Candida* species identified in 27 cases (5.2%).

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When compared with other HSCT subjects, those cultures positive for *Candida* had significantly increased mortality ($p=0.04$).

Conclusions: *Candida sp.* are commonly cultured from the respiratory tract of HSCT recipients, with increased mortality in affected patients. While there is insufficient evidence for anti-fungal treatment of *Candida* species colonization, the presence of the yeast may be useful as a surrogate marker of disease severity.

Summary for Table of Contents:

Candida species are frequently isolated from respiratory tract cultures. The significance of *Candida* colonization of the airway remains unknown. We here propose that *Candida* colonization may be associated with worse outcomes in immunocompromised patients and briefly review the current state of literature in this area.

Keywords

Candida; Respiratory Tract Colonization; Hematopoietic Stem Cell Transplant

Introduction

Candida pneumonia in immunocompetent and immunocompromised patients is rare^{1–3}; however, we propose that the clinical implications of *Candida* isolation from the respiratory tract, particularly in immunodeficient patients, should not be underestimated in regard to increased morbidity or mortality in this particular population. The fungus *Candida albicans* is considered a member of the normal human oral and gastrointestinal microbiome; however, lower respiratory tract colonization in mechanically ventilated immunocompetent patients has been independently associated with longer duration of mechanical ventilation, increased risk of ventilator associated pneumonia, and increased length of intensive care unit (ICU) and hospital stay^{4–6}. A small prospective study of immunocompromised patients found increased mortality in patients with respiratory tract colonization⁷. We now show, in one of the largest retrospective studies to date of hematopoietic stem cell transplant (HSCT) patients, that *Candida* colonization of the airway is associated with worse outcomes.

Methods

We queried the University of Michigan Clinical Microbiology Lab Database for all respiratory cultures positive for *Candida* species between 2000–2012 (University of Michigan IRB HUM00105276). Respiratory cultures reviewed included those from sputum, bronchoalveolar lavage (BAL) fluid, bronchial brushings, washings and biopsies, endotracheal aspirates, and pleural fluid, as well as swabs from the mouth, oropharynx, pharynx or sinuses. Many centers consider *C. albicans* as “normal oral flora” and do not report it in hospital microbiology cultures for immunocompetent patients unless specifically requested.

We then studied a cohort of 515 HSCT recipients at the University of Michigan between 2001–2012 who had radiographic or clinical evidence of pulmonary dysfunction post-transplant, and underwent bronchoscopy with BAL as clinically indicated for their care (IRB

HUM00046894; IRBMED 2001–0234). Subjects were followed for their lifetime, until withdrawal from the study, or until lost to follow up. Pre-HSCT treatment conditioning chemotherapy, stem cell source, donor selection, were administered according to current HSCT guidelines. Unless contraindicated, all transplant recipients received antifungal prophylaxis (fluconazole or voriconazole) and anti-viral prophylaxis according to our center's clinical practice guidelines. Antifungal and anti-bacterial prophylaxis were given for 100 days post-transplant in allogeneic transplant recipients and until engraftment in autologous recipients. Anti-viral prophylaxis was given for 1-year following transplant in all recipients. All allogeneic transplant recipients additionally received prophylaxis against graft versus host disease (GVHD).

Statistical analyses were performed using Chi Square, Fisher's Exact, one-way ANOVA, and Kruskal-Wallis measurements. Kaplan-Meier survival curves were used for all survival analyses with log-rank p-values reported. Data were analyzed using GraphPad Prism 7 (San Diego, CA). The statistically significant difference between groups was assessed at the level of $p < 0.05$.

Results:

Over a 12-year period, 2346 respiratory specimens grew *Candida* species, representing 2524 unique *Candida* isolates. Just under half of all cultures (40.7%) were obtained from sputum or endotracheal aspirate, 23.7% were bronchoscopically obtained, and 17.1% were from the oral cavity. The remaining 20% was comprised of cultures from pleural, nasal, and sinus sources. *Candida albicans* (78%) was the most prevalent species, independent of method of collection, followed by *Candida glabrata* (11%). No other species of *Candida* comprised more than 5% of isolates. 178 specimens (7.6%) grew two or more distinct morphologies or different species of *Candida*. Co-colonization with pathogenic bacteria (7.7%) or fungi (2.3%) was infrequent. Thus, we found that *Candida* species are commonly isolated from respiratory specimens of our hospitalized patients, with *C. albicans* accounting for over 75% of the isolates.

The HSCT cohort included 331 males and 184 females, of which 81% were allogeneic (45.1% related-donor; 54.9% unrelated-donor) and 19% were autologous transplants. The mean age at the time of transplant was 44.25 years (range: 2 months – 75 years; SD 19.95). The most frequent indications for HSCT were Acute Myeloid Leukemia (22.7%), Non-Hodgkins Lymphoma (20.4%), and Multiple Myeloma (10.3%). Additional characteristics of the study group are shown in Table 1. All but two of the patients were followed for greater than one year post-bronchoscopy.

We found that 142/515 (27.6%) HSCT subjects had BAL cultures positive for any fungus, with *Candida* representing 27 cases (5.2% overall). The most commonly isolated species was *C. albicans*, followed by *C. glabrata*. *Candida* spp. were co-isolated with a pathogenic fungus such as *Aspergillus* or *Pneumocystis* in only 4/27 cases. Autologous transplant recipients were significantly more likely than allogeneic transplant recipients to be culture positive for *Candida* in the first 100 days following transplant (75% vs 21%; $p=0.008$). As previously stated, all HSCT patients received anti-fungal prophylaxis with fluconazole or

voriconazole unless contraindicated for 100 days or until engraftment. 5/27 subjects with *Candida* on BAL received new or additional treatment dose anti-fungal therapy for at least 24 hours prior to undergoing bronchoscopy. In this *Candida* positive group, 12/27 patients had known or highly-suspected GVHD at the time of bronchoscopy. Concurrent transbronchial biopsies were obtained in 6/27 patients. Neither *Candida* species, nor evidence of invasive fungal pneumonia were histologically present on any of the biopsies. 1 returned with findings consistent with GVHD.

For our subsequent analyses, we divided the cohort into 4 groups according to BAL culture results: *Candida* isolated (n=27), Non-Pathogenic Fungi isolated (*Candida* negative) (n=57), Pathogenic Fungi isolated (n=58), or Fungal Negative Pneumonitis (n=373). The distinction between pathogenic and non-pathogenic fungi was arbitrated by a transplant infectious disease physician (Table 2). The group with “fungal negative pneumonitis” was defined as having BAL cultures free from any fungal growth but inclusive of cultures positive for viral or bacterial pathogens, as well as sterile cultures. There were no differences in three-year survival between subjects who grew any pathogenic or non-pathogenic fungi in their BAL when compared with those who had “fungal negative pneumonitis” (p=0.45). In contrast, those who had *Candida* isolated from their BAL had significantly increased three-year mortality when compared to patients who had other classically defined “non-pathogenic fungi” (p=0.04; Figure 1a). When compared with the “fungal negative pneumonitis” group, those with *Candida* showed a trend toward increased mortality (p=0.06). There was no statistical difference in three-year mortality between subjects that had BAL fluid cultures positive for pathogenic fungi and those in which *Candida* species were cultured (p=0.24; Figure 1b).

Discussion

To our knowledge, this is the first study to characterize the frequency of *Candida* colonization in the respiratory tract of a heterogeneous population of immunocompromised patients. Asymptomatic colonization of *Candida* in the oropharynx is estimated to occur in 20–50% of healthy individuals, with even higher rates seen in hospitalized and immunocompromised patients^{8–10}. While *Candida* may be frequently isolated from the respiratory tract, it has been well-established that true invasive *Candida* pneumonia is a rare phenomenon in both immunocompetent and immunocompromised patients^{1,2,11–13}. These studies, primarily post-mortem in nature, have shown a poor correlation between positive respiratory cultures and positive histology for invasive *Candida* infection. Consequently, current guidelines do not recommend treatment of respiratory tract *Candida* with anti-fungal drugs. Even so, a great deal of clinical uncertainty remains in how to handle respiratory isolation of *Candida*. In one study, a quarter of ICU physicians stated they would prescribe anti-fungal therapy for an immunocompetent ICU patient with respiratory *Candida* isolated; the same physicians stated they would be even more aggressive in treating an immunocompromised patient¹⁴. Currently, there is no test or threshold able to distinguish between sampling artifact, colonization, or true infection, forcing the clinician to make decisions using clinical judgement.

Recently, a number of animal and human studies have suggested that *Candida* colonization of the respiratory tract, while not directly pathogenic, may contribute to worse outcomes^{4-7,15-22} (Table 3). Studies using rat models of *C. albicans* airway colonization found increased levels of inflammation and prevalence of bacterial pneumonia when compared with controls^{16,20}. Subsequent clinical studies by Hamet et al and Azoulay et al demonstrated associations between *Candida* colonization of the respiratory tract and longer duration of mechanical ventilation, increased length of ICU and hospital stay, and increased risk of ventilator associated pneumonia (VAP) in mechanically ventilated immunocompetent patients^{4,5}. Similar studies conducted in immunocompromised patients have demonstrated that multi-colonization of the oropharynx and gastrointestinal tract is associated with an increased risk of invasive Candidiasis^{18,23} and decreased short term survival⁷. Additionally, a small Dutch study identified a polymorphism in the Dectin-1 gene which was associated with increased susceptibility to fungal infections in HSCT recipients²⁴. Subsequent studies have shown a significant association between *Candida* colonization and the development of acute GVHD in allogeneic HSCT recipients who had Dectin-1 mutations^{25,26}. To date, no study has been able to establish whether *Candida* colonization is a marker of disease severity or is capable of being indirectly pathogenic.

Despite a large body of literature demonstrating a negative relationship between *Candida* colonization of the respiratory tract and patient outcomes, the question of whether to treat *Candida* colonization remains a clinical conundrum. The benefits of prophylactic azoles for the prevention of invasive fungal infections in high-risk HSCT patients has been well-documented,^{27,28} however studies assessing the utility of colonization eradication in both immunocompetent and immunocompromised patients are lacking. To date, two retrospective studies of mechanically ventilated ICU patients with *Candida* colonization have shown conflicting results: one study reported that the use of anti-fungal therapy was associated with significantly reduced development of *P. aeruginosa* pneumonia, while another study found that patients treated with anti-fungal therapy had higher in-hospital mortality and pneumonia rates.^{29,30} A prospective, multi-center, non-interventional study conducted in Spain and Italy found that anti-fungal drugs were more likely to be prescribed in the setting of *Candida* colonization but their use did not alter outcomes.³¹ Unfortunately, interpretation of the above studies is limited by their non-interventional design and the presence of treatment bias. Designed as a pilot trial for feasibility, the CANTREAT trial is the only prospective study undertaken to better elucidate the effects of anti-fungal treatment.³² The study randomized 89 critically-ill adults with suspected VAP and concurrent *Candida* colonization to a placebo-controlled design of anti-fungal therapy. This study did not find any differences in inflammatory markers or hospital mortality between the treatment and placebo groups, and was discontinued prematurely due to slow enrollment leading the authors to conclude that a larger trial could not be supported. To our knowledge, no further prospective trials exploring this question have been undertaken. Resultantly, no clear guidelines for the handling of respiratory tract colonization with *Candida* exist.

Our study has several limitations. The limited sample size of our study prohibited us from performing extensive multi-variate analysis, with only 27 of 515 (5.2%) of BAL positive for *Candida* sp. Additionally, no data was available on cause of death for patients who died. Even so, this is one of the largest studies to date of HSCT recipients. Another limitation of

our study was the potential for patient bias, in which patients too sick to undergo bronchoscopy were not available for analysis, either due to the severity of their pulmonary dysfunction or other clinical features that precluded bronchoscopy. This population of patients would presumably have even higher rates of *Candida* colonization and worse outcomes.³³ Finally, the frequency of *Candida* colonization in our HSCT cohort was significantly lower than previously reported studies, likely due to the routine use of anti-fungal prophylaxis in the study population.³⁴ Though our study showed worse outcomes in those with *Candida* isolated from BAL, it is possible that *Candida* is a surrogate marker of disease severity or a confounding variable in the presence of other conditions such as GVHD or other infection. As such, the observations reported in this study do not support adding anti-fungal therapy for treatment of *Candida* in the respiratory tract.

Conclusion

We now report the incidence of *Candida* spp. colonization in the respiratory tract of a heterogeneous population of immunocompromised patients. Our study adds to the growing body of evidence that calls into question whether *Candida* colonization of the respiratory tract is truly the innocent bystander we have long considered it to be. While there is certainly no evidence at this stage to recommend anti-fungal treatment for colonization, we believe our findings should encourage further, large-enrollment, prospective clinical studies examining the role of *Candida* colonization as a co-factor for disease progression or as a biomarker for disease severity, particularly in an immunocompromised population.

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List of Abbreviations:

(Allo-RD)	Allogeneic Related-Donor
(Allo-URD)	Allogeneic Matched Unrelated-Donor
(BAL)	Bronchoalveolar Lavage
(GVHD)	Graft versus Host Disease
(HSCT)	Hematopoietic Stem Cell Transplant
(ICU)	Intensive Care Unit
(VAP)	Ventilator Associated Pneumonia

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Figure 1: *Candida* isolation from the respiratory tract is associated with increased mortality in immunocompromised patients.

(A) When compared with subjects from which only non-pathogenic fungi were isolated (*Candida* negative group), those who were culture positive for *Candida* had significantly increased mortality ($p=0.04$). (B) There was no statistical difference in mortality between subjects in which a pathogenic fungus was cultured (e.g., *Aspergillus*, *Pneumocystis*, *Mucor*, etc.) and those in which a *Candida* species was cultured ($p=0.24$). Kaplan-Meier survival curves were used for all survival analyses with log-rank p-values reported. Data were analyzed using GraphPad Prism 7 (San Diego, CA).

Table 1.

Demographics

	Candida	Non-Candida Non-Pathogenic Fungi	Pathogenic Fungi	Fungal Negative
	N=27	N=57	N=58	N=373
Age, mean years (range)	44.1 (9.7–67.2)	45.93 (1.0–69.7)	49.5 (4.0–75.3)	44.2 (1.0–72.1)
Sex				
Male	16	43	42	230
Female	11	14	16	143
Transplant Type				
Autologous	8	3	8	79
Allogeneic	19	54	50	294
Donor Source*				
Bone Marrow	2	4	4	42
Peripheral Blood	25	49	51	313
Cord	0	4	3	18*
*1 Bone Marrow + Cord				
Intensity				
Full	24	37	39	295
Reduced	3	20	19	78
Mean days to bronchoscopy	313.4	413.5	317.3	219.5

Table 2:

Classification of Pathogenic vs Non-Pathogenic Fungi

Non-Pathogenic Fungi	Pathogenic Fungi
Arthrographis sp.	Aspergillus sp.
Paecilomyces sp.	Fusarium sp.
Mycelia Sterilia	Pneumocystis
Cladosporium sp.	Scedosporium sp.
Penicillium sp.	Rhizopus sp.
Geotrichum sp.	Mucor
Saprophytic Mold	Cryptococcus sp.
Acremonium sp.	
Scopulariopsis sp.	
Saccharomyces Cerevisiae	
Chaetomium	
Bipolaris sp.	
Trichoderma	
Aureobasidium Pullulans	
Malbranchea sp.	
Nigrospora sp.	
Rhinocladella	
Dematiaceous molds	
Phialemonium sp.	
Phialophora sp.	
Alternaria sp.	

Table 3:

Summary of animal and human studies showing relationship between *Candida* colonization of oropharyngeal or respiratory tract and worse outcomes.

Study	Study Design & Population	Main Findings
Immunocompetent Host		
Roux et al. 2009	Rats intra-tracheally instilled with <i>C. albicans</i> and <i>P. aeruginosa</i>	Respiratory tract <i>C. albicans</i> increased the prevalence of <i>P. aeruginosa</i> pneumonia.
Roux et al. 2013	Rats intra-tracheally instilled with <i>C. albicans</i> , <i>P. aeruginosa</i> , <i>E. coli</i> , and <i>S. aureus</i>	Respiratory tract <i>C. albicans</i> increased lung inflammation and the prevalence of bacterial pneumonia.
Tan et al. 2016	Rats intra-tracheally instilled with <i>C. albicans</i> and <i>Acinetobacter baumannii</i> .	Respiratory tract <i>C. albicans</i> colonization increased the prevalence of <i>A. baumannii</i> pneumonia.
Delisle et al. 2008	Retrospective cohort study of patients with suspected VAP. N=639; 114 with <i>Candida</i> colonization.	Respiratory tract <i>Candida</i> colonization was independently associated with increased hospital mortality.
Delisle et al. 2011	Retrospective cohort study of patients with suspected VAP. N=274; 68 with <i>Candida</i> colonization	<i>Candida</i> respiratory tract colonization was associated with increased ICU and hospital mortality and increased duration of mechanical ventilation and length of stay.
Azoulay et al. 2006	Multi-center, prospective, observational study of mechanically ventilated ICU patients. N=803	Respiratory tract <i>Candida</i> colonization was associated with prolonged ICU and hospital length of stay and increased risk of <i>P. aeruginosa</i> VAP.
Williamson et al. 2011	Prospective observational study in patients with clinical suspicion of VAP. N=595; 21 with <i>Candida</i> colonization.	Respiratory tract <i>Candida</i> colonization was associated with increased levels of systemic inflammation and worse clinical outcomes.
Hamet et al. 2012	Prospective observational study of patients with clinically suspected VAP. N= 323; 181 with <i>Candida</i> colonization.	Respiratory tract <i>Candida</i> colonization was independently associated with increased risk of mortality and multi-drug resistant bacterial pneumonia.
Chotirmall et al. 2010	Prospective observational study of patients with Cystic Fibrosis. N=89; 3916 sputum samples over study period.	<i>Candida</i> colonization predicted occurrence of hospital-treated exacerbations and accelerated rate of decline in body mass index and FEV1.
Gileles-Hillel et al. 2015	Longitudinal study of patients with Cystic Fibrosis. N= 91, 4244 sputum cultures over study period.	Chronic colonization with <i>Candida</i> was associated with lower FEV1 and higher annual rate of decline in FEV1.
Immunocompromised Host		
Martino et al. 1994	Retrospective study of surveillance cultures in neutropenic patients with hematologic malignancies. N=424	Neutropenic patients with multiple body sites colonized with <i>Candida</i> were at increased risk of disseminated <i>Candida</i> infection.
Marr et al. 2000	Retrospective review of HSCT recipients with surveillance cultures. N= 585; 256 with <i>Candida</i> isolated	Oral <i>Candida</i> colonization was associated with three times increased risk of development of Candidemia.
Safdar et al. 2002	Prospective evaluation of <i>Candida</i> colonization in hospitalized cancer and HSCT patients. N= 193; 89 with respiratory tract colonization.	Patients with <i>Candida</i> colonization of multiple body sites had poor survival compared with those who did not.

VAP – Ventilator Associated Pneumonia; ICU – Intensive Care Unit; HSCT – Hematopoietic Stem Cell Transplant