

MINIREVIEW

The significance of *Candida* in the human respiratory tract: our evolving understanding

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One sentence summary: This is a review of what is currently known and yet to be determined about the clinical, microbiological and pathophysiological significance of the detection of *Candida* spp. in the human respiratory tract.

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ABSTRACT

Candida is an opportunistic pathogen and the most commonly isolated fungal genus in humans. Though *Candida* is often detected in respiratory specimens from humans with and without lung disease, its significance remains undetermined. While historically considered a commensal organism with low virulence potential, the status of *Candida* as an innocent bystander has recently been called into question by both clinical observations and animal experimentation. We here review what is currently known and yet to be determined about the clinical, microbiological and pathophysiological significance of the detection of *Candida* spp. in the human respiratory tract.

Keywords: *Candida*; colonization; respiratory tract

INTRODUCTION

Candida species (spp.) are, by far, the most common fungal pathogens in humans. Of the 8%–10% of all nosocomial infections caused by fungal pathogens, 80% are attributable to *Candida* spp. (Edwards 1991). Of the nearly 200 identified species of *Candida*, only 20 have been implicated as a cause of disease in humans (Williams *et al.* 2013). Despite a steady increase in the relative frequencies of infections attributed to non-*Candida albicans* species, *C. albicans* remains the most commonly identified pathogenic member of the genus. Despite its impressive potential for virulence, *Candida* spp. colonize the respiratory tract of half of all healthy individuals, the vast majority of whom are asymptomatic (Baum 1960).

Candida spp. have historically been considered commensal constituents of normal human oral microbiota, with little significance attached to their detection in respiratory specimens. Yet in recent years, both animal experimentation and human observations have provided provocative evidence that *Candida* spp. may represent more than an innocent bystander, both in infectious and non-infectious disease states. The clinical significance of the detection of *Candida* spp. in the respiratory tract is increasingly uncertain. In this review, we summarize what is currently known—microbiologically, pathophysiologically and clinically—regarding *Candida*'s significance in the respiratory tract, and highlight key areas in need of further study.

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BLURRED LINES: CONTAMINATION, COMMENSALISM, COLONIZATION AND CANDIDIASIS

Candida is commonly identified as a constituent of normal human microbiota throughout the body. Frequently detected living on the human epidermis, it can also inhabit the gastrointestinal tract, the genitourinary tract of women and the respiratory tract (Kumamoto and Vinces 2005). Regardless of sampling site, no single test or threshold distinguishes whether the yeast is an artifact of sampling (contamination), benign and native to the patient's microbiota (commensalism), residing in a body site without causing active infection (colonization) or etiologic in an acute infection (candidiasis). Instead, the detection of *Candida* must always be interpreted within its clinical and microbiological context.

Candida albicans—the most abundant and clinically significant representative of the *Candida* genus—has a variety of microbiological traits that equip it with adaptability to colonize the mucosa alongside the bacteria and exist in a 'commensal' or mutualistic state or to become pathogenic and invasive during disease. The presence and behavior of bacterial microbiota are believed to be key in determining *Candida*'s relative virulence. Mucosal-associated bacteria prevent overgrowth of *Candida* via competition for epithelial cell adhesion sites, metabolic interference of hyphal transformation and induction of antimicrobial mechanisms (Huffnagle and Noverr 2013; Hofs, Mogavero and Hube 2016). In the absence of indigenous bacterial microbiota, *Candida* is able to increase in number, infect and invade epithelial surfaces.

Adherence of *Candida* to host surfaces is necessary for initial colonization, contributes to persistence within the host, and may also play an important role during the progression from colonization to infection. Changes in the expression of adherence ligands and receptors may play an important role in the shift from commensalism towards colonization or infection. While initial adhesion likely occurs between *Candida* in its yeast state and epithelial cells, adhesins expressed exclusively on hyphal cells are of great significance for ongoing adhesion (Zhu and Filler 2010; Moyes, Richardson and Naglik 2015). The ability of *Candida* to switch morphologies between a budding yeast and a filamentous hyphal form is its most important virulence trait, and is known to be regulated both by a variety of environmental stimuli as well as the presence of quorum-sensing molecules (Biswas, Van Dijck and Datta 2007; Han, Cannon and Villas-Boas 2011). Compared with its yeast state, the hyphal form of *Candida* exhibits increased adherence properties, invasiveness and greater pathogenicity (Kimura and Pearsall 1980; Odds 1988). The ability of *Candida* to secrete hydrolytic enzymes that digest molecules for nutrient acquisition and cause tissue damage also contributes to its virulence. These secreted enzymes contribute to host invasion by digesting host surface molecules to enhance

adhesion or to distort host cell membranes allowing for deeper invasion (Cannon et al. 1995). Finally, loss of epithelial integrity or deficiencies in innate host immune mechanisms may allow for *Candida* colonization or infection to prevail. Prominent risk factors for acquisition of *Candida* in the respiratory tract include exposure to antibiotics, critical illness, immune compromised status, use of mechanical ventilation and hospital or intensive care unit stay (Table 1) (Fidel 2002; Perlroth, Choi and Spellberg 2007; Lalla et al. 2010; Moore et al. 2010; van de Veerdonk et al. 2011; Hofs, Mogavero and Hube 2016; Krause et al. 2016).

Though we have known for decades that *Candida* colonizes the mouth of even healthy individuals, both its temporal persistence within individuals and the extent of its presence in the lower respiratory tract remain unsettled questions. When *Candida* is isolated on a single occasion from a given host reservoir, clinicians cannot know with confidence if this represents transient presence or persistent colonization. Older studies attempted to address this question in specific regard to oral colonization of *Candida* and concluded that carriage was continuous in the overwhelming majority of subjects with *Candida* detected (Lilienthal 1950; Williamson 1972). In most current studies and practice, colonization is pragmatically defined as detection of *Candida* from one or more samples from a surveillance site; however, no consensus definition exists at this time. Rates of *Candida* carriage in the human mouth vary widely by study, ranging from 20% to 50% among asymptomatic healthy individuals, with even higher rate of carriage in hospitalized patients (Baum 1960; Morales and Hogan 2010). In an early and influential study by Baum (1960), the majority of hospitalized patients had *Candida* detectable in their sputum. The authors arrived at two key conclusions that have shaped the body of *Candida* literature since their time. First, since the healthy tracheobronchial tree was considered a sterile environment, they inferred that *Candida* detected in the sputum of healthy individuals must reflect contamination of sputum as it passes through the mouth during expectoration. Second, they concluded that due to the frequency of isolation of *Candida albicans* in both healthy and diseased subjects, little clinical significance could be attached to the finding of *Candida* in the sputum.

Regarding this first conclusion (the absence of *Candida* in the lungs of healthy individuals), our understanding of the sterility of the lower respiratory tract has been revolutionized in the past decade by the rise of culture-independent microbiology and the dawn of the lung microbiome field. Using culture-independent techniques, numerous groups have detected diverse communities of microbes in the lungs of healthy individuals, and features of the lung microbiome have been correlated with the presence and prognosis of numerous respiratory diseases (Dickson et al. 2016). These studies, largely focused on bacteria, have prompted reconsideration of the assumption that *Candida* and other fungi are absent from healthy lungs. Recent studies have used

Table 1. Major risk factors for acquisition of *Candida* in the respiratory tract.

Host factors	Latrogenic causes	Immunosuppression	Extraneous
Genetic factors including (STAT1 and dectin-1 mutations)	Broad spectrum antibiotics	Neutropenia	Prolonged hospital stay
	Mechanical ventilation	Steroid use HIV	ICU stay Burns
	Radiation therapy	Diabetes mellitus Bone marrow or solid organ transplant Use of systemic immunosuppression	

molecular techniques to re-address whether the finding of *Candida* in the oral cavity reflects *Candida* in the lower respiratory tract. In a recent study by Krause et al. (2016), detection of *Candida* in the oral cavity correlated poorly with its detection in the lower respiratory tract as sampled directly from either endobronchial tubes or bronchoscopically. Despite detection of *Candida* from the oral specimens of 29% of healthy volunteers, *Candida* was essentially absent from the lower respiratory tract of healthy subjects, whether tested using conventional culture (87 subjects) or culture-independent means (four subjects). Thus, despite the increased sensitivity of modern culture-independent techniques, we still have no direct evidence that *Candida* is present in the lower respiratory tract of healthy individuals.

METHODS USED IN ISOLATION AND IDENTIFICATION OF CANDIDA

Currently, clinical laboratory identification of *Candida* in the respiratory tract relies upon the successful recovery of species from culture. No culture-based or molecular test of respiratory specimens can distinguish between contamination, colonization and invasive disease. Despite ongoing advances in culture-independent techniques for identification of other respiratory pathogens, fungal culture remains the 'gold standard' for the identification of *Candida* spp., regardless of sampling site. *Candida* spp. grow well on a variety of commonly used culture media, but most frequently Sabouraud's glucose agar and broth are used. Colonies of *Candida* generally grow between 25°C and 37°C and have a smooth to wrinkled texture and a white to beige color on Sabouraud's agar (Calderone 2002). Media containing chromogenic compounds may be useful in the detection of clinically important *Candida* spp. including *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei* and *C. dubliniensis* as colonies grown on such agars may be distinguished according to color (Odds and Bernaerts 1994). While culture can provide both definitive identification and speciation of a fungus, it lacks sensitivity, and time to fungal growth is lengthy. Additional factors affecting isolation of *Candida* spp. from respiratory specimens include previous exposure to antimicrobial therapy as well as technical factors including volume of sample, culture media used, incubation time and temperature (World Health Organization 2000). Direct microscopic examination, another method of detection for samples such as bronchoalveolar lavage (BAL) fluid, is more sensitive than culture, but utilization is limited as it requires expertise for interpretations and distinguishes poorly among fungi with similar morphology.

Given the poor sensitivity of culture, studies have begun to investigate non-culture-based modalities for identification of *Candida* in the respiratory tract. The 1,3- β -D-glucan assay detects soluble fungal wall components released during fungal growth and division (Bowman and Free 2006). It has demonstrated decent performance as a screening test for invasive fungal infections within the bloodstream, but its utility in BAL fluid is unproven. The largest relevant study to date, a retrospective review, demonstrated poor consistency and specificity using 1,3- β -D-glucan for the detection of invasive fungal infections of the lung in BAL specimens (Rose et al. 2014). Furthermore, the 1,3- β -D-glucan assay is unable to distinguish between *Candida* and other fungi, further limiting its clinical utility as a diagnostic test. Additional studies have examined the use of latex agglutination in BAL fluid to test for the presence of *Candida* antigens as well as the use of polymer-based chain reaction (PCR) for molecular identification of *Candida* isolates with mixed results

(Ness et al. 1988; Zarrinfar et al. 2016). Currently, no methods for the identification of *Candida* in the respiratory tract, aside from standard culture, have garnered enough evidence or momentum to be adopted into clinical practice. Further investigations into methods of reliably identifying *Candida* within a timely fashion, or distinguishing between colonization or invasive candidiasis, would be a welcome contribution to the field.

DOES CANDIDA CAUSE PNEUMONIA?

True invasive *Candida* pneumonia is so rare in immunocompetent patients that its very existence is debated. When it occurs, it is attributed either to seeding of the lungs from hematogenous dissemination or (less likely) to aspiration of colonized oropharyngeal or gastric contents (Meersseman et al. 2009). Definitive diagnosis of pulmonary *Candida* infection depends on histologic demonstration of yeast as well as inflammatory cells in lung tissue. The diagnosis of *Candida* pneumonia is challenging, as histology is rarely available clinically, and less invasive means fail to distinguish infection (a rarity) from colonization (which is common). Numerous studies have demonstrated that the incidence of *Candida* isolation from pulmonary biopsies or BAL fluid in critically ill mechanically ventilated patients is around 40%–50%, whereas the incidence of true *Candida* pneumonia is considerably lower (el-Ebiary et al. 1997; Meersseman et al. 2009; Hamet et al. 2012). An informative study by el-Ebiary et al. (1997) demonstrated that *Candida* colonization of the lungs occurs in roughly 40% of immunocompetent critically ill patients, based on rigorous post-mortem histologic examination. Comparison of tissue diagnoses with pre-mortem, clinically available information was revealing: only 9% of BAL cultures from the same patients grew *Candida*, and only 2 patients out of 25 in the study had definitive *Candida* pneumonia confirmed by histology. Two other prospective studies have confirmed the frequency of *Candida* spp. colonization in mechanically ventilated critically ill patients (present in more than half (53%–56%) of patients (Meersseman et al. 2009; Hamet et al. 2012) while showing that true *Candida* pneumonia is rarely—if ever—present histologically.

CANDIDA: MERELY AN INNOCENT BYSTANDER?

Based on these clinical observations, and aligned with the second conclusion of Baum et al. (that little significance can be attached to the finding of *Candida* in the sputum of healthy or diseased patients), *Candida* pneumonia is rare if ever present, and when *Candida* is detected in respiratory specimens it is generally considered an 'innocent bystander' (Ricard and Roux 2012). Yet recent experimental and clinical observations have suggested that even if not directly pathogenic, *Candida* may still contribute indirectly to respiratory disease. In their study of 803 patients across six ICUs, Azoulay et al. (2006) studied the significance of *Candida* isolation from respiratory specimens in critically ill patients. Respiratory tract *Candida* colonization was associated with a longer duration of mechanical ventilation and increased length of ICU and hospital stay. Provocatively, they found a significant, independent association between respiratory tract *Candida* colonization and ventilator-associated pneumonia due to *Pseudomonas aeruginosa*. Interestingly, no association was found between *Candida* colonization and other bacterial pathogens that commonly cause ventilator-associated pneumonias, a finding which may be attributed to the small number of patients included in that analysis. A subsequent

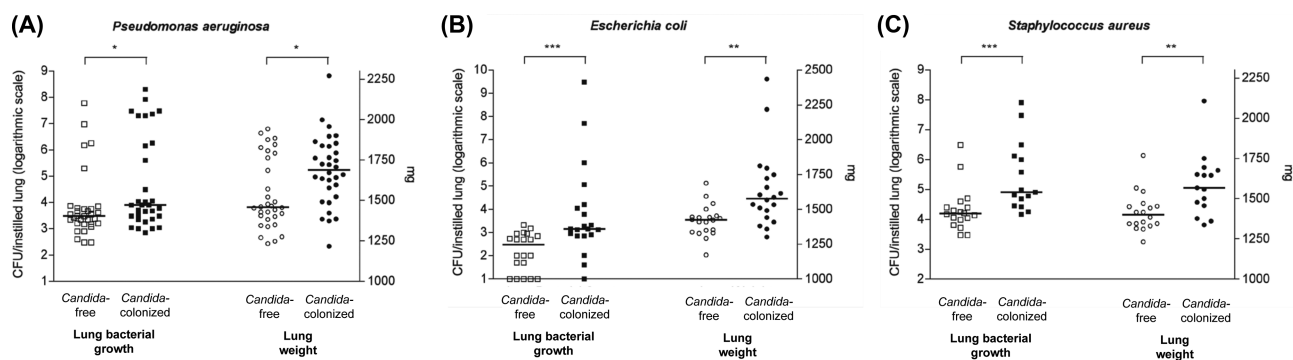


Figure 1. *Candida* colonization of the airway potentiates bacterial pneumonia in a rat model. *Pseudomonas aeruginosa* (A), *E. coli* (B) and *S. aureus* (C) were instilled into the tracheas of rats with and without prior instillation of *C. albicans*. With all three pathogens, *C. albicans* significantly worsened both bacterial burden and lung injury. Figure reproduced from Roux *et al.*

retrospective analysis performed on 639 patients with suspected VAP revealed a significant increase in median hospital stay and mortality in patients who harbored *Candida* in their respiratory tract when compared to those that did not (Delisle *et al.* 2008). Detection of *Candida* in respiratory specimens was independently associated with a 2.5-fold increase in mortality. A similar retrospective analysis again confirmed that among patients with suspected VAP, detection of *Candida* in the absence of bacterial pathogens was predictive of increased ICU and hospital mortality, longer duration of mechanical ventilation and increased hospital length of stay (Delisle *et al.* 2011). The same association between *Candida* isolation and mortality was found by Hamet *et al.* (2012); furthermore, *Candida* colonization was an independent predictor for co-isolation of multidrug-resistant bacteria. These effects could not be ascribed to invasive *Candida* infection, as none were observed during the study periods.

Why then, if *Candida* does not cause pneumonia, does detection of *Candida* in the respiratory tract of critically ill patients consistently portend increased morbidity and mortality? An intuitive explanation is that *Candida* colonization is the proverbial canary in the coal mine: a marker of disease severity and dysregulation of the host immune system. Yet a myriad of animal studies examining fungal–bacterial mixed inoculation suggest a more direct role in disease pathogenesis. The findings of a representative study by Roux *et al.* are shown in Fig. 1. In rodent models of pneumonia, a given inoculum of *P. aeruginosa* in the respiratory tract unable to cause bacterial pneumonia on its own can indeed provoke infection when co-instilled with *C. albicans* (Roux *et al.* 2009). This effect is not observed when ethanol-killed *C. albicans* is inoculated, indicating that *Candida* must be alive to potentiate *P. aeruginosa*'s virulence. This observation has held true across bacterial pathogens, including *Staphylococcus aureus* and *Escherichia coli* (Roux *et al.* 2013) (Fig. 1).

The notion of a synergistic effect between *Candida* species and bacterial pathogens has been explored previously. While both *in vivo* and *in vitro* studies have lent plausibility to a synergistic relationship between *C. albicans* and *P. aeruginosa*, the relationship is not limited to these two pathogens (Hogan and Kolter 2002; Peleg, Hogan and Mylonakis 2010). Early studies in mice found that dual infection with *C. albicans* and *S. aureus* led to overall increased mortality when compared to infection with either pathogen in isolation (Carlson 1982). More recent work has examined the synergistic relationship between *S. aureus* and *C. albicans* as it pertains to biofilm formation. *Staphylococcus aureus* more readily forms biofilms in the presence of *C. albicans* than in its absence, and more readily demonstrates antibiotic resis-

tance within these polymicrobial biofilms (Harriott and Noverr 2009).

The mechanisms behind *Candida*'s potentiation of bacterial pneumonia in animal models remain incompletely understood despite burgeoning research into the effects of *Candida* colonization on host immunity. Airway colonization with *Candida* alone is associated with increased levels of TNF- α and IFN- γ within the lung, even in the histological absence of acute infection (Roux *et al.* 2009). Co-inoculation with *Candida* and *P. aeruginosa* further elevate alveolar concentrations of TNF- α , IFN- γ and IL-6. As IFN- γ is capable of impairing function of alveolar macrophages (Sun and Metzger 2008), some have hypothesized that the presence of *C. albicans* in the airways can induce an immune response that inhibits the normal antibacterial function of host immune cells, allowing bacterial pathogens to evade clearance and initiate infection.

The interaction between *Candida* and bacterial respiratory infection is not limited to mechanically ventilated, critically ill patients nor animal models of pneumonia. A growing body of literature in cystic fibrosis (CF) patients has shown that *Candida* is the dominant fungal genus comprising the respiratory microbiome of these patients, and that of this genus *C. albicans* is the dominant species. To date, two longitudinal studies examining the effects of respiratory colonization with *Candida* in CF patients have been conducted with similar results. Colonization with *C. albicans* occurs commonly (~50%) in CF patients and is associated with the presence of pancreatic insufficiency, osteopenia or co-colonization with *P. aeruginosa* (Chotirmall *et al.* 2010). Chronic respiratory colonization with *C. albicans* is associated with impaired lung function, the trajectory of worsening lung function, unintentional weight loss and increased frequency of hospital-treated exacerbations (Gileles-Hillel *et al.* 2015).

TO TREAT OR NOT TO TREAT?

Despite this considerable literature demonstrating that detection of *Candida* in the respiratory tract is associated with increased risk of bacterial pneumonia, multidrug-resistant pathogens, and morbidity and mortality, the clinical utility of eradication of *Candida* with antifungal drugs remains a matter of debate. Animal studies have demonstrated that antifungal treatment in the setting of respiratory colonization with *Candida* significantly decreased susceptibility to bacterial pneumonia with attenuated lung inflammation (Venkatesh *et al.* 2007; Roux *et al.* 2013). A second study, in neonatal rats septic from co-infection with *Candida* and *Staphylococcus epidermidis*, showed

enhanced survival in the setting of fluconazole prophylaxis (Venkatesh et al. 2007). These promising results from experimental models of pneumonia have prompted retrospective and prospective human studies to determine the clinical utility of treating respiratory *Candida* with antifungal therapy.

Retrospective data on the question have proven provocative but conflicting. A French study of 102 mechanically ventilated patients with tracheobronchial *Candida* colonization found that antifungal therapy was the only variable independently associated with significantly reduced risk of development of *Pseudomonas aeruginosa* pneumonia (Nseir et al. 2007). Yet a larger German study instead found that patients treated with antifungal therapy had higher in-hospital mortality and pneumonia rates than those who did not (Lindau et al. 2015). A recent third study found no association between antifungal therapy and favorable clinical outcome (Terraneo et al. 2016). These retrospective and non-interventional studies are inescapably limited by potential confounding: patients who receive antifungal therapy are quite certainly subject to treatment bias, as patients harboring respiratory tract *Candida* disproportionately have risk factors for invasive fungal infection, immunosuppression or higher severity of illness. In the setting of these conflicting and confounded results, no firm treatment guidelines have been established, and clinical practice varies widely.

In light of the discrepancy between animal and clinical studies assessing the utility of antifungal drug use in the setting *Candida* airway colonization in ICU patients, a feasibility study was recently undertaken. The CANTREAT trial is the largest randomized, placebo-controlled trial to date aimed at evaluating inflammatory profiles and clinical outcomes in *Candida* colonized patients with clinically suspected VAP (Albert and Heyland 2014). It enrolled a total of 89 patients and was designed to determine the feasibility of a large-scale, randomized controlled trial. At baseline, TNF-alpha levels were higher in patients with suspected VAP in the setting of *Candida* colonization compared to those with clinically suspected VAP in the absence of *Candida* airway colonization. Following at least 72 h of antifungal therapy or placebo, no differences were found in either inflammatory marker profiles or hospital mortality between the groups. Unfortunately, the study was discontinued prior to reaching target enrollment due to slow recruitment, and the authors concluded that a larger randomized controlled trial was likely not feasible. As outlined by other critics of the study, the CANTREAT trial had many limitations (Roux and Ricard 2014). First, the study was designed for feasibility, not to definitively answer this clinical question, and was thus underpowered for this purpose. Furthermore, patients enrolled already had presumed VAP in the setting of *Candida* airway colonization; thus, its results tell us nothing regarding the effects of antifungal therapy in preventing or attenuating early VAP in at-risk patients. At this time, no prospective studies have been undertaken to evaluate this question.

CONCLUSIONS

Though provocative animal experimentation suggests that *Candida* is more than an innocent bystander in the respiratory tract, no clinical data to date provides support for its treatment in colonized patients. Further study into fungal-bacterial interactions and the potentiation of bacterial pneumonia are needed, and prospective human studies into the efficacy of treating colonization are justified. The final word on *Candida*'s significance in the respiratory tract has yet to be spoken.

Conflict of interest. None declared.

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