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Candida Spp. in the Respiratory Tract

Silvia Terraneo, MD
******@***unimi.it

Physician - Respiratory Unit Ospedale San Paolo Department of Health Science Università degli Studi di Milano, Milan, Italy

Miquel Ferrer, MD, PhD, FERS
******@***clinic.cat

Physician - Department of Pneumology Respiratory Institute Hospital Clinic, IDIBAPS University of Barcelona Barcelona, Spain CibeRes-ISCiii (CB06/06/0028)

Antoni Torres, MD, PhD, FERS
******@***clinic.cat

Professor of Medicine - Head, Respiratory Intensive Care Unit Department of Pneumology Respiratory Institute Hospital Clinic, IDIBAPS University of Barcelona Barcelona, Spain. CibeRes-ISCiii (CB06/06/0

A Real Causality With Worse Outcomes or Just a Marker of Severity?

- *Candida* spp. is the most common cause of intensive care unit (ICU) invasive fungal infections worldwide.
- The isolation of *Candida* spp. from respiratory tract secretions of non-immunocompromised, mechanically ventilated patients varies between 20% and 55%, but it might represent colonisation rather than infection.
- *Candida* spp. colonisation promotes bacterial pneumonia in animal models.
- *Candida* spp. colonisation could clinically increase the risk for *Pseudomonas aeruginosa* ventilator-associated pneumonia, prolong mechanical ventilation and stay and worsen outcomes, but to date contrasting data are available.
- Available evidence is not sufficient to support routine antifungal therapy in non-immunocompromised patients.

Candida spp. is part of the normal skin, oropharyngeal, mucosal membranes and upper respiratory tract flora. *Candida* spp. can reach the lungs through either haematogenous dissemination or aspiration of colonised oropharyngeal or gastric contents (Muray et al. 1977). The isolation of *Candida* spp. from respiratory tract secretions is frequent in nonimmunocompromised, mechanically ventilated patients. Several studies have reported the presence of *Candida* spp. in the sputum of 20-55% of patients receiving antibiotics (Azoulay et al. 2006; Delisle et al. 2008). *Candida* spp. is the most common cause of invasive fungal infections, with an incidence estimated at 72.8 cases per million inhabitants per year (Guinea 2014). The five main species of *Candida* spp (*C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. tropicalis* and *C. krusei*) are responsible for more than 90% of invasive fungal infections, in both intensive care unit (ICU) and non-ICU patients (Maubon et al. 2014). *Candida* pneumonia is a rare lung infection with a high morbidity and mortality, commonly observed as part of a disseminated *Candida* infection and associated with predisposing clinical circumstances (i.e. long-term antibiotic use, haematologic malignancy or severe immunosuppressive states). The majority of *Candida* pneumonia cases are secondary to haematological dissemination of *Candida* spp. (Masur and Rosen 1977). There is no specific clinical or radiological presentation of *Candida* pneumonia. This aspect of the disease makes the diagnosis difficult to perform. A definitive diagnosis of *candida* pneumonia is now based on histopathological identification of yeast parenchymal invasion with associated inflammation.

Significance of *Candida* Spp. Isolation in Non-Immunosuppressed Patients

Invasive lung infection by *Candida* spp. is a rare event in non-immunocompromised subjects. Several studies showed that the recovery of *Candida* spp. from sputum and other respiratory tract secretions cultures or lung tissue in nonimmunocompromised patients might represent colonisation of the tracheobronchial tree rather than infection.

El-Elbiary et al. (1997) performed an autopsy study on 25 immunocompetent, mechanically ventilated patients, who died in a medical ICU, in order to assess the real significance of *Candida* spp. presence in the tracheobronchial tree or lungs. Immediate postmortem respiratory samples and lung tissue specimens were microbiologically and histologically examined. The incidence of *Candida* spp. isolation from pulmonary biopsies

was 40%, while the incidence of *Candida* pneumonia was only 8%. The presence of *Candida* spp. in pulmonary biopsies was always associated with the isolation of the same microorganism from one of another respiratory sample. Furthermore there was a uniform presence of *Candida* spp. throughout the different lung regions, but the fungal isolation, independently of quantitative cultures, was not recognised as a good marker of *Candida* pneumonia (el-Ebiary et al. 1997).

In 2009 Meersseman et al. performed a similar study. Data from autopsies of patients, who died in a medical ICU and with evidence of pneumonia, were analysed in order to define the value of *Candida* spp. isolation in airway samples of those patients. Histopathological evidence of pneumonia was found in 58% of patients. Of these, 57% had positive tracheobronchial samples for *Candida* spp. performed during the preceding two weeks. No cases of *candida* pneumonia were identified amongst those cases or in patients without *Candida* isolation. These results confirmed that the presence of *Candida* spp. in respiratory samples does not indicate pneumonia and that this is an extremely rare event in ICU patients (Meersseman et al. 2009).

Candida Spp. Colonisation as Risk Factor for _P. Aeruginosa_ Ventilator-Associated Pneumonia OR Multi-Drug Resistant Bacteria

Although the diagnosis of isolated *Candida* pneumonia is rare, the presence of *Candida* spp. on pathological samples should not be clinically ignored. *P. aeruginosa* and *Candida* spp. are among the most prevalent organisms in ICU-acquired infections (Vincent et al. 1995), and they could coexist in the endotracheal tube or medical devices biofilm of patients (Adair et al. 1999). These two pathogens have physical, chemical, environmental and phylogenetic similarities (Ader et al. 2008; Hogan and Kolter 2002). The question of how they interplay in the respiratory tract has been investigated, with contrasting results, in animal studies.

Ader et al. (2011) showed that *P. aeruginosa* lung injury was reduced in the presence of *C. albicans* in a mouse model, as well as the amount of alive *P. aeruginosa* recovered in lungs. Antifungal treatment with caspofungin removed this effect in those cases. However, mortality rate and bacterial dissemination did not vary between colonised and not colonised animals (Ader et al. 2011).

Conversely, in 2009 Roux et al. performed a randomised controlled animal study with the aim of determining the effect of *C. albicans* presence on *P. aeruginosa* pneumonia. *P. aeruginosa* was instilled in the tracheobronchial tree of animals with or without previous *C. albicans* tracheobronchial colonisation. Animals with *C. albicans* tracheobronchial colonisation developed more frequently *P. aeruginosa* pneumonia compared with those without. In addition, higher levels of proinflammatory cytokines (TNFα, IFγ, IL-6) were measured in the lungs of animals instilled with *P. aeruginosa* with previous *C. albicans* colonisation, compared with those without *C. albicans* colonisation (Roux et al. 2009).

In addition a preliminary report showed that *C. albicans* colonisation favours the occurrence of pneumonia related to *S. aureus* and *E. coli* (Roux et al 2009). Similarly, a recent study suggests that fungal colonisation also facilitated the development of *Acinetobacter baumanii* pneumonia in a rat model, with a protective role of antifungal therapy on this event (Tan et al. 2016). Thus the mechanism by which *Candida* spp. colonisation promotes bacterial pneumonia could be independent of bacterial species.

ICU-acquired pneumonia (ICUAP) is the leading infection in critically ill patients, accounting for prolonged mechanical ventilation and length of stay, poor outcome and excess costs. There is evidence of interactions between *Candida* spp. and *P. aeruginosa*, with fungal colonisation possibly increasing the risk for *P. aeruginosa* infection. Some clinical reports have shown a possible association between the presence of *Candida* spp. in respiratory secretions and an increased risk for *P. aeruginosa* ventilatorassociated pneumonia (VAP), longer mechanical ventilation, prolonged stay and worse outcomes.

In a cohort of immunocompetent mechanically ventilated patients, Azoulay et al. (2006) found the isolation of *Candida* spp. in the tracheobronchial tree as an independent risk factor for pneumonia, due to *P. aeruginosa*. *Candida* spp. colonisation was not associated with higher mortality, but colonised patients showed a significantly longer time on ventilation, and longer ICU and hospital stays compared to patients without *Candida* spp. isolation from the respiratory tract.

Candida spp. has been identified as a risk factor for multidrug-resistant bacteria. Hamet et al. 2012)) conducted a prospective observational study in order to investigate the significance of *Candida* spp. airway colonisation in patients with suspected VAP and the potential link with isolation of multidrug-resistant (MDR) bacteria. Fifty-six percent of patients with suspected VAP had *Candida* spp. airway colonisation. *Candida* spp. airway colonisation was an independent risk factor for MDR bacteria isolation without significant differences in aetiological pathogens. Colonised patients were similar to non-colonised patients regarding VAP severity; however, in this study mortality rate was greater in patients with fungal airway colonisation than in those without (Hamet et al. 2012).

In a retrospective analysis of the Canadian VAP study, Delisle et al. (2008) found *Candida* spp. isolation in respiratory samples in 17.8% of all patients. Colonised patients showed longer hospital stay than non-colonised patients and a significant increase in hospital mortality. In that population *Candida* spp. presence was independently associated with hospital mortality. Antibiotic administration, co-morbidities and a more severe illness are probable factors associated to *Candida* spp. isolation (Delisle et al. 2008; Terraneo et al. 2016).

In 2015 we performed a prospective noninterventional study in a medical and surgical ICU of a teaching hospital. The purpose of this study was to compare the characteristics, microbiology, inflammatory response and outcomes of patients diagnosed with ICUAP (mechanically ventilated or not), with and without *Candida* spp. presence in lower respiratory tract samples, and to assess the characteristics and outcomes associated with the antifungal therapy. We conducted the study in view of the discrepancy between the uncertain clinical relevance of the isolation of *Candida* spp. in respiratory tract secretions and its association with adverse clinical outcomes in patients with VAP.

Candida spp.-colonised patients showed higher severity scores than patients without airways fungal colonisation, but similar inflammatory pattern. Clinical outcomes were similar between colonised and non-colonised patients, including 28-day and 90-day mortality, with the exception of an increased risk of intubation in patients with *Candida* sp. colonisation (Terraneo et al. 2016).

See Also: Infections in the Immunosuppressed and Immunocompromised Patient

Antifungal Treatment

Although *Candida* spp. is frequently isolated from respiratory tract samples, antifungal treatment is not routinely recommended, because pneumonia caused by this fungal species is exceptional in non-neutropenic patients (Garnacho-Montero et al. 2013). Inappropriate use of antifungal treatment could be associated with higher rates of fungal resistance and mortality in ICU patients; therefore, *Candida* spp. isolation from respiratory secretions alone should not be promptly treated (Cuenca-Estrella 2012; Rello et al. 1998). Nevertheless antifungal therapy is frequently prescribed for immunocompetent mechanically ventilated patients with isolation of *Candida* spp. from respiratory tract samples (Azoulay et al. 2004; van der Geest et al. 2014). The effect of antifungal therapy in patients with *Candida* spp. airways colonisation has been extensively studied with discordant results.

A retrospective case-control study conducted by Nseir et al. (2007) showed that the prescription and length of the antifungal treatment were associated with a reduced risk for *P. aeruginosa* VAP development or tracheobronchial isolation in mechanically ventilated patients colonised by *Candida* spp.

Wood et al. (2006) performed a retrospective study in trauma ICU patients. *Candida* spp. was isolated from 8% of diagnostic bronchoalveolar lavages (BALs). Most of the isolations were considered colonisation and no specific therapy was prescribed. No patients developed candidaemia or serious fungal infections after isolation of *Candida* spp., despite the lack of antifungal therapy. Furthermore, *Candida* spp. was not isolated in subsequent follow-up BALs. No significantly greater mortality rate was observed in patients with a high level of *Candida* spp. in BAL, despite the lack of therapy (Wood et al. 2006).

In 2014 van der Geest et al. (2014) performed a retrospective analysis of non-neutropenic mechanically ventilated patients with positive *Candida* spp. cultures of the respiratory tract treated or not with amphotericin-B deoxychlorate inhalation therapy in the context of selective decontamination of the digestive tract. Treated patients did not decolonise more rapidly as compared to untreated patients. The duration of mechanical ventilation was increased by treatment independently of *Candida* spp. presence, suggesting a direct toxicity of the drug in the lung. No differences in VAP development or overall mortality were observed in this study (van der Geest et al. 2014).

In 2014 Albert et al. performed a double-blind, placebo-controlled, multicentric, pilot randomised clinical trial in order to evaluate inflammatory profiles and clinical outcomes of patients with suspected VAP and *Candida* spp. presence, treated or not with antifungal therapy. The isolation of *Candida* spp. was associated with persistent inflammation and immunosuppression, but markers of inflammation and all clinical outcomes had similar results between patients treated and not treated with antifungal therapy, both at baseline and over time (Albert et al. 2014).

In our study we observed a more frequent prescription of antifungal therapy in patients with evidence of *Candida* spp. in respiratory tract samples or patients with multiple co-morbidities or a more severe illness. However, in our group of patients, antifungal therapy was not associated with different outcomes in patients with *Candida* spp. in respiratory samples (Terraneo et al. 2016).

Conclusion

Despite the frequent isolation of *Candida* spp. from respiratory specimen of ICU patients, the development of real candida pneumonia is very unlikely when immunocompetent subjects are considered. However, the presence of *Candida* spp. in pathological samples should not be clinically ignored because it could probably be associated with a more severe illness. What remains unsolved is the question about a real causality between *Candida* spp. and worse outcomes, since *Candida* spp. could be simply a marker of severity. As of today, available evidence is not sufficient to support routine antifungal therapy in these patients. In addition, further studies are required to understand the real impact of *Candida* spp. on respiratory infection development and patients' outcomes and consequently the possible protective role of antifungal agents' administration.

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Conflict of Interest

Silvia Terraneo, Miquel Ferrer and Antoni Torres declare no conflict of interest.

Abbreviations

BAL bronchoalveolar lavage

ICU intensive care unit

ICUAP intensive care unit-acquired pneumonia

MDR multidrug-resistant

VAP ventilator-associated pneumonia

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