Cover Story
The Abdomen

Plus
Point-of-Care Test Devices in the ED
Redesigning Ambulatory Emergency Care with Point-of-Care Testing
Candida Spp. in the Respiratory Tract
Vasoactive Drugs in Sepsis

Controversies in VAP Diagnosis
Monitoring Peripheral Circulation
Touch Creates a Healing Bond in Healthcare
Women in Leadership in Intensive Care Medicine

Intensive Care Syndrome: Promoting Independence and Return to Employment
Burden Caused by Administrators and Managers
Interview: Prof. Gernot Marx, University Hospital Aachen
Country Focus: Brazil
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 non-immunocompromised, 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 non-immunocompromised 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. isolation 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-Elbiary 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 pro-inflammatory cytokines (TNFα, IPα, 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 baumannii 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.

**further studies are required to understand the real impact of Candida spp. on respiratory infection development and patients’ outcomes**

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* ventilator-associated 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 non-interventional 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).

**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 (Cuencastrella 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 deoxycholate 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.

Acknowledgments

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

Abbreviations
BAL bronchoalveolar lavage
ICUAP intensive care unit
ICUAP intensive care unit-acquired pneumonia
MDR multidrug-resistant
VAP ventilator-associated pneumonia

References

©For personal and private use only. Reproduction must be permitted by the copyright holder. Email to copyright@mindbyte.eu.