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EDITORIAL

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Candida colonization of respiratory tract: to treat or not to treat, will we ever get an answer?

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In non-immunocompromised intensive care unit (ICU) patients *Candida* isolation from various sites is common [1]. The association with the risk of invasive candidiasis (IC) is the rational for the use of predictive scores which include the colonization status.

However the meaning of *Candida* spp. recovery from the lung is definitely more intriguing. Apart from IC episodes occurring in deeply immunosuppressed subjects who may develop true fungal pneumonia, *Candida* respiratory tract (RT) isolation should not be considered a marker of lung infection. This issue was addressed by Meersseman et al. [2] who did not identify any autopsy-proven case of *Candida* pneumonia among 135 autopsies with histopathological evidence of bacterial infection and high rate of *Candida* isolation from endotracheal aspirate (EA) and/or bronchoalveolar lavage (BAL) (57 %).

However there is growing convincing evidence, based on animal studies and human observations, that *Candida* spp. is not definitely an innocent bystander in the respiratory tract of ICU ventilated patients [3–13] (Table 1). Beta-glucan (BG), a component of yeast cell wall, may act as a lung proinflammatory agent causing alveolar macrophage and neutrophil dysfunction. Additionally, within the environmental biofilm there is a strong interplay, through quorum-sensing (QS) molecules, between *Candida* and both Gram-positive and Gram-negative bacteria [14]. Live *Candida albicans* instillation in rats has been observed to increase the susceptibility to develop experimental *Pseudomonas aeruginosa* (PA), *Escherichia coli* (Ec), and *Staphylococcus aureus* (Sa) pneumonia, fostering the production of lung inflammatory cytokines (tumor necrosis factor alpha [TNF-alpha], interleukin-6 [IL-6], and interferon-gamma [INF-γ]) and inhibiting alveolar macrophage phagocytosis [3, 5]. From a clinical viewpoint, *Candida* airway colonization has been shown to be associated with prolonged duration of mechanical ventilation, ICU/hospital length of stay, and increased mortality [8–11]. One of the first reports of this possible relationship dates back to almost 10 years ago, when Azoulay et al. [6] identified *Candida* bronchial isolation as an independent risk factor for the development of PA ventilator-associated pneumonia (VAP) (9 vs 4.8 % in non-colonized patients, $p = 0.048$). These data were strengthened just 1 year later by Nseir et al. [7] who observed a protective role of antifungal treatment on PA VAP occurrence in a cohort of patients with *Candida* tracheobronchial colonization. However, recently, the use of nebulized amphotericin B (NAB) was not able to provide any clinical improvement, albeit increasing the rate of *Candida* decolonization (adjusted HR 2.2; 95 % CI 1.6–3) [13]. Hence the clinical usefulness of respiratory tract *Candida* colonization (CC) eradication in mechanically ventilated patients is still a matter of debate and the paper by Albert et al. [15] in the current issue of *Intensive Care Medicine* is the first interventional trial aiming to describe the biochemical and clinical effect of antifungal treatment in ICU patients with VAP and RT *C*c. In this double-blind, placebo-controlled, multicenter study 60 patients were enrolled: 29 in the placebo group and 31 in the antifungal strategy group. A comparative

observational cohort of 29 patients with VAP but without *Candida* respiratory colonization was also included. No differences between the two arms were found in any of the investigated clinical outcomes: maximum and delta Sequential Organ Failure Assessment (SOFA) score, MV- and ICU-free days, subsequent ICU-acquired infections, and day-28, day-90, and hospital mortality. In addition, the inflammatory profile (TNF-alpha, IL-6, IL-8, IL-10, IL-1B, C-reactive protein [CRP], procalcitonin [PCT], intestinal fatty acid binding protein (iFABP), and lipopolysaccharide [LPS]-stimulated TNF-alpha) was similar between the antifungal and the placebo group, not being influenced by the assigned treatment. On the other hand patients harboring *Candida* spp. in the RT, compared with the observational group, showed higher TNF-alpha values (21.8 ± 23.1 vs. 12.4 ± 9.3 pg/mL, $p = 0.02$) and lower LPS-induced TNF-alpha production capacity (854.8 ± 855.2 vs. $1{,}559.4 \pm 1{,}290.6$ pg/mL, $p = 0.01$). Unfortunately, because of the slow enrollment rate (0.6 patients per month per site for the intervention groups), the trial was interrupted long before the completion of the planned sample size (120 patients for the randomized trial and 40 for the observational cohort). The authors' conclusion excluded the feasibility of a larger phase 3 trial aiming to assess the potential benefits of the antifungal treatment in patients with concomitant RT *Candida* spp. and VAP but some aspects of this interesting study deserve further investigation.

First, one important issue might be the choice as inclusion criteria of clinically suspected VAP (csVAP), rather than microbiologically confirmed cases. Only in 14 out of 60 randomized patients (six in the placebo arm and eight in the intervention arm) were the respiratory specimens positive for pathogenic bacteria and only two Pa isolates were observed.

Clinical diagnosis of VAP is challenging: in ventilated patients chest X-ray images may be frequently misleading and about 30 % of ICU-acquired pneumonia remains without etiology. The authors previously described that patients with RT *Candida* colonization and csVAP may experience similar inflammation burden and worse outcome than patients with bacterial infections [11]. Airway *Candida* colonization is associated with pulmonary inflammation and consequent cellular immune dysfunction, but the role of biofilm and fungal-bacterial cross-talk should not be neglected.

Candida biofilm consists of a network of yeasts, hyphae, and/or pseudohyphae embedded in a matrix of polysaccharides, proteins, and other undefined components. This status results in the protection of the fungi

Table 1 Main animal and human studies on RT *Cc* and bacterial pneumonia relationship

References	Study design	Study population	Main findings
Roux et al. [3]	Experimental animal investigation	88 Wistar rats (70 instilled with *Candida* and Pa)	RT *Cc* reduced AM ROS production ($p < 0.001$) and increased Pa pneumonia prevalence ($p < 0.01$)
Ader et al. [4]	Experimental animal investigation	24 BALB/c mice instilled with Pa, *Candida* or both	Pa lung injury was reduced by prior RT *Cc* ($p < 0.05$). This effect was reversed by caspofungin administration
Roux et al. [5]	Experimental animal investigation	200 Wistar rats with RT *Cc* (98 instilled with Pa or Ec or Sa)	Previous RT *Cc* favored the development of Pa, Sa, and Ec pneumonia ($p < 0.05$)
Azoulay et al. [6]	Nested exposed/unexposed study	605 pts (211 with RT *Cc*)	CC was associated with increased Pa VAP risk (9 vs 4.8 %, $p = 0.04$)
Nseir et al. [7]	Retrospective case–control study	57 pts (19 with Pa VAP)	Antifungal treatment reduced the risk of Pa VAP (OR 0.68, 95 % CI 0.49–0.9, $p = 0.046$)
Delisle et al. [8]	Retrospective cohort study	639 pts (114 with RT *Cc*)	RT *Cc* increased the risk of hospital mortality (RR 1.63, 95 % CI 1.20–2.21, $p = 0.003$)
Williamson et al. [9]	Prospective observational study	170 pts (21 with csVAP/RT *Cc*)	RT *Cc* in csVAP was associated with lower number of ICU-free days and greater mortality ($p < 0.05$)
Heyland et al. [10]	Prospective observational study	57 pts (12 with csVAP/RT *Cc*)	Trend to higher BG levels in RT *Cc* group ($p = 0.09$). BG positivity was associated with increased 28-day mortality ($p = 0.03$)
Delisle et al. [11]	Retrospective exploratory analysis	274 pts (68 with *Cc* RT/VAP)	*Candida* spp. was associated with increased hospital mortality ($p < 0.001$)
Hamet et al. [12]	Prospective observational study	323 pts (181 with *Cc* RT/csVAP)	CC RT was an independent risk factor for MDR bacteria isolation (OR 1.79, 95 % CI 1.05–3.05, $p = 0.03$)
Ong et al. [13]	Observational cohort study	333 episodes of RT *Cc* episodes (59 received NAB)	NAB reduced the *Cc* RT duration by approximately 3 days, without any improvement in clinical outcomes

RT respiratory tract, *CC Candida* colonization, *Pa Pseudomonas aeruginosa*, *Sa Staphylococcus aureus*, *Ec Escherichia coli*, *AM* alveolar macrophages, *ROS* reactive oxygen species, *VAP* ventilator-associated pneumonia, *BG* beta-glucan, *MDR* multidrug-resistant, *NAB* nebulized amphotericin B, *pts* patients

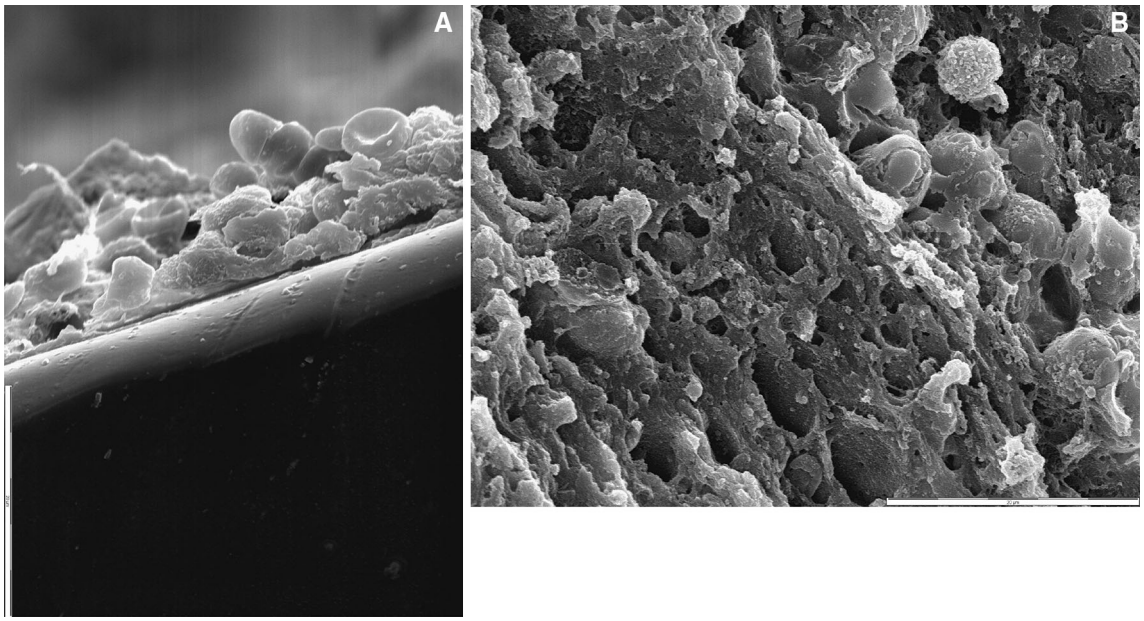

Fig. 1 Scanning electron microscopy of an uncoated endotracheal tube after extubation (**a** luminal surface, **b** bacterial biofilm) [16]

from the host defenses and the development of antifungal drug resistance. Many bacteria are able to produce biofilm and studies using electron microscopy showed that Pa, *Enterobacteriaceae* (including Ec), Sa, and *Candida* spp. are the most common pathogens collected from artificial airways of mechanically ventilated patients (Fig. 1) [16]. Despite billions of years of cross-kingdom interaction, little is know about *Candida*–bacteria interactions within the biofilm. A wide range of metabolic processes and cell-to-cell communications through QS molecules are the basis of both synergistic and antagonistic interactions. Interestingly, in a prospective observational study, RT *Cc* was identified as an independent predictor of multidrug-resistant bacteria airway isolation in patients with suspected VAP [12]. As a result of the exiguous number of microbiologically confirmed VAP in the CANTREAT study, no conclusions may be drawn about these phenomena.

Second, Albert et al. [15] did not provide details on biofilm production of isolated *Candida* spp. A recent survey of ICU patients with IC reported in 297 *Candida* isolates, percentages of biofilm formation ability ranging between of 20 and 50 % and higher mortality rates in patients with candidemia may be observed in the presence of high producers strains [17]. In the CANTREAT trial, patients in the intervention group received anidulafungin for a mean of 5.9 ± 3 days but only 22.6 % were not sequentially switched to fluconazole. Unlike fluconazole, echinocandin and liposomial amphotericin B are highly active against both planktonic and biofilm *Candida* spp. but, despite the high 72 h *Candida* eradication rate, we are not aware of the potential beneficial anti-biofilm effects derived from the use of anidulafungin.

Third, the authors investigated in detail the inflammatory profile of enrolled subjects. Patients with csVAP and RT *Cc* were distinctly characterized by an increased inflammatory status and a relative immunosuppression; however, this pathophysiological condition did not change over antifungal treatment, as well as BG serum levels. It is noteworthy that the average BG levels were fairly low and mainly in the range of possible false positive results [18]. In addition, the fungicidal properties of anidulafungin might have determined an early BG release from the yeast cell wall, influencing the kinetics of this biomarker and of the local/systemic inflammatory response.

Finally, the very restrictive inclusion criteria together with a relevant percentage of excluded patients (72 out 133, 54.1 %) contributed to the premature interruption of the trial, which did not reach the predetermined sample size.

A definitive conclusion on the clinical relevance of respiratory tract *Candida* colonization has not yet been reached, and at present data are still insufficient to recommend the routine use of antifungals as decolonizing agents in non-immunocompromised patients.

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