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EDITORIAL

Jean-Damien Ricard
Damien Roux

Candida colonization in ventilated ICU patients: no longer a bystander!

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J.-D. Ricard · D. Roux
Institut National de la Santé et de la Recherche Médicale (INSERM) U722, 16 rue Henri Huchard, 75018 Paris, France

J.-D. Ricard · D. Roux
Université Paris Diderot, Sorbonne Paris Cité, UMRS 722, 75018 Paris, France

J.-D. Ricard (✉)
Service de Réanimation Médicale,
AP-HP, Hôpital Louis Mourier, 92700 Colombes, France
e-mail: jean-damien.ricard@lmr.aphp.fr
Tel.: +33-1-47606750
Fax: +33-1-47606192

D. Roux
Channing Laboratory, Department of Medicine,
Brigham and Women's Hospital, Harvard Medical School,
Boston, Massachusetts, USA

The role and consequences of the presence of *Candida* spp. in the lungs of mechanically ventilated patients are receiving growing attention as we gain insight into the interaction between fungi and bacteria in diseases in general [1] and in lung infection in particular [2]. In a 2009 issue of *Intensive Care Medicine*, Meersseman et al. provided us with convincing data on the absence of *Candida* pneumonia in the ICU despite a high rate of colonization (53 %) [3]. These authors could however only speculate on the significance of the presence of *Candida* spp. in their patients. We ended our accompanying editorial by stating that *Candida* lung colonization may have a significant role in bacterial pneumonia development [4]. This statement was prompted by several clinical and experimental clues.

Azoulay et al. were among the first to hypothesize that the presence of *Candida* spp. in the airways of mechanically ventilated ICU patients might not be anecdotal [5]. In their study, *Candida* colonization was associated with an increased risk for *Pseudomonas aeruginosa* ventilator-associated pneumonia (VAP). Another important hint towards the role of *Candida* spp. was provided by Nseir et al. [6], who showed that antifungal treatment decreased the risk for *P. aeruginosa* infection in colonized patients. An experimental validation to these clinical observations was later provided by the demonstration that when challenged with an inoculum of *P. aeruginosa* insufficient to induce bacterial pneumonia, rats colonized with *C. albicans* developed considerably more *P. aeruginosa* pneumonia that non-colonized rats [2]. The question that then arose was whether this effect was specific to *P. aeruginosa*? A preliminary experimental report suggested that colonization also favored the development of *Staphylococcus aureus* and *Escherichia coli* pneumonia [7], implying that the mechanisms by which *Candida* colonization promoted bacterial pneumonia were independent of bacterial species. Such an observation had not been made in the clinical field, probably because, given the prevalence of *P. aeruginosa*, studies were not powered enough to detect an effect on other bacteria.

In this issue of *Intensive Care Medicine*, Hamet et al. [8] provide further evidence for the significant role played by *Candida* colonization in bacterial VAP.

These authors studied all clinically suspected VAP episodes in their ICU during a 4-year period and reviewed the microbiological data for the presence of *Candida* spp. colonization, bacterial documentation of the VAP episode

and resistance profile to antibiotics. A total of 323 episodes were analyzed. Important confirmatory but also unexpected interesting findings were obtained.

First of all, Hamet et al. confirm that *Candida* spp. colonization is frequent in mechanically ventilated patients, since more than half (56 %) of their patients harbored *Candida* in their airways, a figure very similar to the 53 % reported by Meersseman et al. [3], underlying the frequency of this phenomenon.

Second, they also confirm that *C. albicans* is the most frequently isolated yeast (56 %), in perfect agreement with Meersseman et al. (55 %)!

Unexpected, or at least unpublished so far, was the observation that *Enterobacteriaceae* were the most frequently isolated pathogens (25.1 %), quite ahead of *P. aeruginosa* (16.7 %) and way above *S. aureus* (13.3 %). These findings differ from the common knowledge that *P. aeruginosa* is the most frequent pathogen responsible for VAP and lend support to the growing importance in ICU infections of *Enterobacteriaceae* in general and *E. coli* in particular [9].

The authors also reported that 31.5 % of bacteria isolated in patients with *Candida* spp. colonization were multidrug resistant (MDR) versus 23.2 % in non-colonized patients ($p = 0.13$). In the univariate analysis, isolation of MDR bacteria was associated with antibiotic exposure. Since previous studies found an association between airway *Candida* colonization and previous antibiotic exposure [5, 10, 11], it is probable that the association between MDR bacteria and *Candida* colonization reported by Hamet et al. [8] is more likely due to shared risk factors than causal association.

Perhaps the most striking result of the Hamet et al. [8] study is the association found between *Candida* spp. airway colonization and increased mortality in mechanically ventilated immunocompetent critically-ill patients (44 % in colonized patients vs. 31 % in controls); this remained true after adjustment of other variables in a logarithmic regression model including SAPS II and age. This cannot be explained by actual fungal infection because no candidemia were observed during the whole period of this study. Even if no causal link can be raised, it is interesting to observe that previous clinical studies comparing the same set of patients (i.e., immunocompetent critically ill patients under mechanical ventilation with or without *Candida* colonization) showed the same trend. Azoulay et al. observed a mortality of 43 % in colonized patients and 36 % in controls (univariate analysis: $p = 0.067$) [5]. Delisle et al. found the same observation with a mortality of 34 vs. 21 % in colonized and control patients, respectively ($p = 0.003$) [10]. This was still the case in a logistic regression model that included age, comorbidities and admission for neurological disorders as co-variables.

So how can one explain this increased mortality in the context of airway *Candida* colonization? The first obvious answer is *Candida* colonization is simply a marker of severity that the retrospective design of the studies cited above cannot distinguish from cofounders despite ajustments performed in the analysis. Otherwise, two non-mutually exclusice hypotheses can be raised. The first is a modification in bacterial virulence and/or host immunity [1]. Back in the 1980s, Carlson showed that dual intraperitoneal injection of *C. albicans* and *S. aureus* at doses that separately caused no animal deaths resulted in 100 % mortality [12]. Interestingly, after this fungal-bacterial mixed inoculation, bacteria were highly predominant in peripheral organs. The latter was observed for gram-negative and gram-positive pathogenic bacteria, and even after a very small bacterial inoculum if the *Candida* inoculum was maintained [13]. These data suggest that the presence of *C. albicans* protects bacteria against normal clearance and enhances their virulence. In vitro, many studies have highlighted the importance of cross-kingdom communication, especially between fungus and bacteria [1]. If *P. aeruginosa* can influence the morphology of *C. albicans* with one of its quorum-sensing molecules (N-acyl homoserine lactones), the opposite is also true. Farnesol, which is *C. albicans* main quorum sensing molecule, is able to influence the motility and the expression of virulence factors of *P. aeruginosa* [14]. The second hypothesis is an indirect effect of *Candida* via the local and systemic inflammatory response to *Candida* colonization. Indeed, the presence of *Candida* spp. in airways of ventilated patients with suspected VAP (but without actual infection) is associated with an increased systemic inflammation as compared to control patients [11]. Inflammation has been associated with an increased risk of infection and mortality during ARDS [15], at least in part because of the enhanced growth, and possibly virulence, of pathogenic bacteria [15, 16]. Inflammation elicited by *Candida* colonization may also affect the immune defense, which in turn favors bacterial development. We developed a murine model of airway *Candida* colonization using single or iterative intratracheal instillations of clinical or laboratory strains of *C. albicans* [2, 17]. This model is consistently characterized by a Th1-Th17 immune response with very high pulmonary levels of interferon-gamma [17]. We showed that alveolar macrophages were unable to phagocyte gram-negative or gram-positive pathogenic bacteria after culture with this cytokine. Consequently, the incidence of bacterial pneumonia was higher in this context of fungal airway colonization as compared to control animals. Finally, an antifungal treatment was able to normalize the cytokine levels and prevent the development of bacterial pneumonia [17].

Taken together, Hamet et al.'s [8] study adds further evidence to the influence of *Candida* colonization in mechanically ventilated ICU patients. Clearly, *Candida* spp. should no longer be seen as a simple bystander and may constitute possible leads for new therapies to treat pneumonia [18, 19]. But in this case, the questions that

remain unanswered are: should we give antifungal treatment to these colonized patients in order to decrease VAP and possibly mortality; when should we start it, and which drug should we use? But that's another story.

Conflicts of interest JDR and DRs' experimental research laboratory received a research grant by Pfizer to study bacterial and fungal interactions in the lungs.

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