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EDITORIAL

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Candida pneumonia in the ICU: myth or reality?

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Ventilator-associated pneumonia (VAP) remains the leading cause of nosocomial infection in the ICU despite increasing efforts to reduce it. Although most, if not all, VAP is due to bacteria, the role, if any, of fungal pathogens is unclear in immunocompetent hosts [1]. Indeed, many studies have reported the presence of *Candida* species in the lungs of immunocompetent, ventilated patients [2–4], but the extent to which this presence is linked to authentic fungal pneumonia remains debated. Several reasons may account for these uncertainties. First of all, the diagnosis of pneumonia in mechanically ventilated patients is difficult whatever the microorganism. Clinical criteria for suspecting VAP are unspecific and microbial confirmation may, in some instances, be subject to caution [1]. Second, some microbiology laboratories do not pursue the study of fungi when rapidly growing yeasts are found in respiratory samples. Third, if for bacteria the threshold of 10^3 or 10^4 CFU/mL for protected brush specimens or BAL, respectively, is now widely accepted to confirm VAP, no such threshold has been established for fungi. There is thus no gold standard routine method to diagnose *Candida* pneumonia and the most accepted method relies on lung histology. Taken together, it is usually accepted that *Candida* lung infection is quite rare in the ICU and that *Candida* spp. in respiratory specimens should not be treated unless there is clear histological evidence for such an infection. Because histological sampling of the lung is rarely performed (whether it be during lung biopsy or on autopsy); it is possible that *Candida* pneumonia remains unrecognized and hence under-diagnosed. The alternative is that *Candida* pneumonia is simply not encountered in the ICU. This may be regarded as a futile debate. However, when presented with a clinical vignette of a mechanically ventilated patient with positive respiratory samples for *Candida*, a substantial number of physicians would give antifungal treatment [5]. Given the high incidence of *Candida*-positive respiratory specimens in ventilated, ICU patients; this attitude may lead to excessive treatment, undue costs, and risk of increased resistance to antifungal agents. Although autopsy studies in cancer patients have identified some cases of *Candida* pneumonia, exhaustive and convincing data in ICU patients is lacking. In this issue of Intensive Care Medicine, Meersseman and colleagues provide clear (and definite?) evidence for the absence of *Candida* pneumonia in ICU patients [6]. Over a two-year period, they were able to perform post-mortem examinations on 77% of their patients. It is indeed routine practice in their

institution to perform autopsies for all patients who die in the ICU. This is already, in itself, an accomplishment for which authors should be commended! On the basis of the results of routine tracheal surveillance cultures, patients were classified as having or not *Candida* spp in their respiratory tract. Diagnosis of *Candida* pneumonia was established using a predefined procedure for pathologic examination of the lungs and rigorous histological criteria that included the presence of both pseudohyphae and budding yeasts with various amounts of acute inflammation. Patients were then divided into four groups: positive *Candida* samples and pneumonia at autopsy, positive samples no pneumonia, negative samples with pneumonia at autopsy, and negative samples no pneumonia. With these definitions, no single case of *Candida* pneumonia was found among the 232 patients autopsied, even in those ($n = 77$) with pre-mortem positive samples for *Candida* spp and histological signs of pneumonia. In these patients, *C. albicans* was the most common species identified (55%). Overall rate of *Candida* colonization in the whole population study (taking into account those without pneumonia at autopsy) was high, 53%. Antifungal therapy was used in only seven patients (9%) with *Candida* spp in their airways, so the risk that unrecognised *Candida* pneumonia was successfully treated is limited. One may argue that pneumonia was not seen, simply because the study was underpowered. Given the high incidence of *Candida* colonization, one of the highest in the literature, and the number of patients with pneumonia, this possibility seems unlikely. Meersseman et al. [6] thus provide convincing data on the absence of *Candida* pneumonia. Rather than waiting for yet another study to confirm this, the next question could be why does *Candida* colonization not lead to pneumonia? It is beyond the scope of this editorial to provide an in-depth explanation, but several points deserve attention. Recognition of *Candida* species by professional phagocytes depends on a variety of receptors that are expressed on their surface, for example Toll-like receptors (TLR), mannose receptor, dendritic cell-specific adhesion molecule, and Dectin-1 [7]. Knowing which receptors bind to the organism is important in determining the host immune response. TLR2 and TLR4 recognize *C. albicans* and modulate the host defense. Recognition of the fungus in its yeast form by these TLRs induces mainly a Th1 cytokine pattern with high levels of IFN-gamma and TNF-alfa [8]. This response controls the pathogen [9, 10]. In addition, other experiments show that IFN-gamma favors the intracellular killing of the fungus after internalization in professional phagocytes [11]. Conversely, only TLR2 is able to recognize the hyphae form of *C. albicans* and induces the release of Th2 cytokines with high levels of anti-inflammatory cytokine IL-10 but no IFN-gamma. Such a pattern favors the dissemination of the fungus [8]. Moreover, the mode of antigen presentation affects the development of the Th subsets and presentation by macrophages favored the generation of Th1 cells [12]. Thus, because pulmonary macrophages constitute the first defense line against *C. albicans*; one possible clue for the absence of *Candida* pneumonia could be that *Candida* predominates in its yeast form in the respiratory tract of ICU patients, thereby yielding a Th1 response enabling control of the fungi.

The question that then arises is what to do when confronted with a positive sample for *Candida* spp. Although the results from the Meersseman et al. [6] study confirm that antifungal treatment should not be given with the intention of treating putative *Candida* pneumonia, should the presence of *Candida* simply be ignored? Several hints in the clinical field and more definite experimental data indicate that the answer might be no. Indeed, a retrospective study found that mechanically ventilated patients colonized with *Candida* spp. in the airways were at increased risk of *P. aeruginosa* VAP [13] whereas another that colonized patients that had received antifungal therapy had reduced the risk of *P. aeruginosa* lung infection [14]. In the experimental field, we were interested in studying the impact of *C. albicans* colonization in rats on subsequent *P. aeruginosa* pneumonia development [15]. The most striking observation of our study was that a *P. aeruginosa* inoculum that did not lead to bacterial pneumonia, did so in the presence of *C. albicans* in the airways [15]. This facilitating effect exerted by *C. albicans* was found to be mediated—at least in part—by a decrease in ROS production by alveolar macrophages in the presence of *C. albicans*. Preliminary data from our team further indicate that this facilitating effect is also observed with two other major bacteria responsible for VAP (*Staphylococcus aureus* and *Escherichia coli*) [16]. Keeping with this line of reasoning, Meersseman et al. found that more than half (57%) of the patients with bacterial pneumonia on autopsy were colonized with *Candida* spp. Thus, although it seems evident that the entity "*Candida* pneumonia" is very rare in the ICU, *Candida* lung colonization may have a significant role in bacterial pneumonia development. Future clinical studies will have to assess the benefit of preemptive antifungal treatment of colonization in the perspective of bacterial VAP prevention.

References

1. Chastre J, Fagon JY (2002) Ventilator-associated pneumonia. Am J Respir Crit Care Med 165:867–903
2. Kollef MH, Ward S (1998) The influence of mini-BAL cultures on patient outcomes: implications for the antibiotic management of ventilator-associated pneumonia. Chest 113:412–420
3. Chastre J, Trouillet JL, Vuagnat A, Joly-Guillou ML, Clavier H, Dombret MC, Gibert C (1998) Nosocomial pneumonia in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 157:1165–1172
4. Heyland DK, Cook DJ, Marshall J, Heule M, Guslits B, Lang J, Jaeschke R (1999) The clinical utility of invasive diagnostic techniques in the setting of ventilator-associated pneumonia. Canadian Critical Care Trials Group. Chest 115:1076–1084
5. Azoulay E, Cohen Y, Zahar JR, Garrouste-Orgeas M, Adrie C, Moine P, de Lassence A, Timsit JF (2004) Practices in non-neutropenic ICU patients with *Candida*-positive airway specimens. Intensive Care Med 30:1384–1389
6. Meersseman W, Lagrou K, Spriet I, Verbeken E, Peetermans W, Van Wijngaerden E (2009) Significance of the isolation of *Candida* species from airway samples in critically ill patients: a prospective, autopsy study. Intensive Care Med (in press). doi: 10.1007/s00134-009-1482-8.
7. Filler SG (2006) *Candida*-host cell receptor–ligand interactions. Curr Opin Microbiol 9:333–339
8. van der Graaf CA, Netea MG, Verschueren I, van der Meer JW, Kullberg BJ (2005) Differential cytokine production and Toll-like receptor signaling pathways by *Candida albicans* blastoconidia and hyphae. Infect Immun 73:7458–7464
9. Gozalbo D, Gil ML (2009) IFN-gamma in *Candida albicans* infections. Front Biosci 14:1970–1978
10. Puccetti P, Romani L, Bistoni F (1995) A TH1-TH2-like switch in candidiasis: new perspectives for therapy. Trends Microbiol 3:237–240
11. Watanabe K, Kagaya K, Yamada T, Fukazawa Y (1991) Mechanism for candidacidal activity in macrophages activated by recombinant gamma interferon. Infect Immun 59:521–528
12. Gajewski TF, Schell SR, Nau G, Fitch FW (1989) Regulation of T-cell activation: differences among T-cell subsets. Immunol Rev 111:79–110
13. Azoulay E, Timsit JF, Tafflet M, de Lassence A, Darmon M, Zahar JR, Adrie C, Garrouste-Orgeas M, Cohen Y, Mourvillier B, Schlemmer B (2006) *Candida* colonization of the respiratory tract and subsequent pseudomonas ventilator-associated pneumonia. Chest 129:110–117
14. Nseir S, Jozefowicz E, Cavestri B, Sendid B, Di Pompeo C, Dewavrin F, Favory R, Roussel-Delvallez M, Durocher A (2007) Impact of antifungal treatment on *Candida–Pseudomonas* interaction: a preliminary retrospective case-control study. Intensive Care Med 33:137–142
15. Roux D, Gaudry S, Dreyfuss D, El-Benna J, de Prost N, Denamur E, Saumon G, Ricard JD (2009) *Candida albicans* impairs macrophage function and facilitates *Pseudomonas aeruginosa* pneumonia in rat. Crit Care Med 37:1062–1067
16. Roux D, Gaudry S, Khoy-Ear L, Denamur E, Dreyfuss D, Ricard JD (2009) *Candida albicans* airway colonization favors bacterial pneumonia. [abstract E77]. Am J Respir Crit Care Med 179:A3269