

# Candida Colonization of the Respiratory Tract and Subsequent Pseudomonas Ventilator-Associated Pneumonia\*

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**Background:** Recovery of *Candida* from the respiratory tract of a critically ill patient receiving mechanical ventilation (MV) usually indicates colonization rather than infection of the respiratory tract. However, interactions between *Candida* and bacteria, particularly *Pseudomonas*, have been reported. Thus, *Candida* colonization of the respiratory tract may predispose to bacterial ventilator-associated pneumonia (VAP).

**Methods:** In a multicenter study of immunocompetent critically ill patients receiving MV for > 2 days, we compared the incidence of pneumonia in patients with and without (exposed/unexposed) respiratory-tract *Candida* colonization, matched on study center, admission year, and MV duration.

**Results:** Over the 4-year study period, of the 803 patients meeting study inclusion criteria in the six study centers, 214 patients (26.6%) had respiratory tract *Candida* colonization. *Candida albicans* was the most common species (68.7%), followed by *Candida glabrata* (20.1%) and *Candida tropicalis* (13.1%). Extrapulmonary *Candida* colonization was more common in exposed patients (39.7% vs 8.3%,  $p = 0.01$ ). Exposed patients had longer ICU and hospital stays but similar mortality to unexposed patients. The matched exposed/unexposed nested cohort study identified bronchial *Candida* colonization as an independent risk factor for pneumonia (24.1% vs 17.6%; adjusted odds ratio [OR], 1.58; 95% confidence interval [CI], 0.94 to 2.68;  $p = 0.0860$ ); the risk increase was greatest for *Pseudomonas* pneumonia (9% vs 4.8%; adjusted OR, 2.22; 95% CI, 1.00 to 4.92;  $p = 0.049$ ).

**Conclusions:** *Candida* colonization of the respiratory tract is common in patients receiving MV for > 2 days and is associated with prolonged ICU and hospital stays, and with an increased risk of *Pseudomonas* VAP. (CHEST 2006; 129:110–117)

**Key words:** *Candida*; mechanical ventilation; pneumonia; *Pseudomonas*; ventilator-associated pneumonia

**Abbreviations:** CI = confidence interval; LOD = logistic organ dysfunction; MV = mechanical ventilation; OR = odds ratio; SAPS II = simplified acute physiology score; VAP = ventilator-associated pneumonia

*Candida albicans* is an opportunistic pathogen frequently found in the normal microflora of the human body. Recovery of *Candida* from the respiratory tract of a critically ill patient receiving mechanical ventilation (MV) without risk factors for immunodepression is common.<sup>1</sup> Clinical studies<sup>2,3</sup> into the clinical relevance of “positive” unprotected or protected, proximal or distal, specimens from ICU patients after > 2 days of MV have shown a poor

correlation between *Candida*-positive respiratory samples (colonization) and invasive pulmonary candidiasis. In most patients, lung biopsy or lung autopsy specimens showed tracheobronchial colonization without evidence of invasive pulmonary candidiasis despite respiratory specimen *Candida* counts above the thresholds used to define bacterial nosocomial pneumonia. In one study,<sup>2,3</sup> alveolitis was found in several patients, but there was

no evidence of a causal relation with *Candida*, since other organisms were usually present also. Bronchial *Candida* colonization did not lead to excess mortality but resulted in longer ICU and hospital stay durations, as well as in higher management costs.<sup>4</sup> However, it has been suggested that bronchial *Candida* colonization in patients receiving MV should be interpreted in the light of the colonization index, as colonization of multiple body sites is a risk factor for systemic candidiasis.<sup>4-6</sup>

Studies have found evidence of interactions between *Candida* and *Pseudomonas*, with *Candida* colonization possibly increasing the risk for *Pseudomonas* infection. In the European Prevalence of Infection in Intensive Care study, Vincent<sup>1</sup> determined the prevalence of ICU-acquired infections and identified the predominant organisms. *Pseudomonas aeruginosa* and *Candida* species were among the most prevalent organisms (28.7% and 17.1%, respectively). Similarly, *Candida* and *Pseudomonas* were among the most common pathogens retrieved from endotracheal tube biofilm and tracheal secretions in patients with ventilator-associated pneumonia (VAP).<sup>7</sup> Moreover, El-Azizi et al<sup>8</sup> reported that *C albicans* biofilms could hold other organisms, including *P aeruginosa*, within the endotracheal tube. Using an experimental burned-mouse model, Neely and colleagues<sup>9</sup> showed that recent *Pseudomonas* infection increased the risk of fatal candidiasis. Molecular studies<sup>10</sup> identified phylogenetic similarities between the two pathogens, and Hogan et

al<sup>11,12</sup> reported that *Candida* morphology and virulence were significantly affected by the presence of *P aeruginosa*.

To look for an association between *Candida* colonization of the respiratory tract and subsequent *Pseudomonas* VAP, we performed a data collection of *Candida* colonization in immunocompetent critically ill patients who received MV for > 2 days. We compared the incidence of VAP in patients with *Candida* colonization of the respiratory tract (exposed group) and in paired, matched control subjects (unexposed group).

## MATERIALS AND METHODS

### *The Outcomerea Database*

The Institutional Review Board of the French Society of Critical Care approved the inclusion of critically ill patients in the Outcomerea database. Patients and family members gave their informed consent that anonymous data would be collected and entered into the database. We conducted a prospective observational study in the multicenter Outcomerea database, which is specifically designed to record daily disease severity and occurrence of iatrogenic events and nosocomial infections. Between January 2000 and December 2003, *Candida* colonization was prospectively collected in a selected subsample of the Outcomerea database. All patients > 18 years old requiring > 2 days of MV were included. We excluded patients with immunodeficiency (HIV infection, neutropenia, solid cancer, hematologic malignancy, solid-organ or bone marrow transplantation, or long-term [> 3 months] or high-dose [> 1 mg/kg] steroid treatment).

All six study ICUs followed the same management protocol for nosocomial pneumonia and *Candida* colonization and infection. This protocol was not changed for the present study. Clinically suspected nosocomial pneumonia was routinely documented using cultures of protected distal specimens, protected brushing, or BAL, as previously described.<sup>13,14</sup> Antibiotic treatment of nosocomial pneumonia was in compliance with current guidelines.<sup>13,14</sup> Invasive candidiasis was defined as recommended.<sup>15</sup> Recovery of *Candida* spp from the lungs (protected or unprotected specimens), urine, stool, upper digestive tract (mouth, pharynx, or stomach), drainage systems, or postoperative sites was interpreted as colonization, regardless of organism counts. When *Candida* was documented at one body site, specimens were collected routinely from other sites to look for additional *Candida* colonization. Antifungal therapy was at the discretion of the physician in charge.<sup>16</sup>

### *Data Collection*

Data were collected daily on computers by ICU physicians closely involved in establishing the database. All codes and definitions were written before data collection. For each patient, the ICU physician completed a case report form on a computer using data capture software (Vigirea; manufactured by author's group) and then imported all records to the database. The following information was recorded prospectively: demographic characteristics (age, sex, weight, height); underlying diseases using the McCabe score and Knaus classification<sup>17</sup>; presence of diabetes mellitus (with the type and complications); admission category (medical, scheduled surgery, or unscheduled surgery);

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†The members of the Outcomerea study group are listed in the Appendix.

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admission diagnosis (cardiac, respiratory, or neurologic failure, infection, and other); invasive procedures (arterial or venous central catheter, Swan-Ganz catheter, endotracheal intubation); and treatment of organ failures (inotropic support, hemodialysis, and mechanical ventilation). Location of the patient prior to ICU admission was recorded, with transfer from wards defined as being in the same hospital or another hospital before ICU admission. Severity of illness was recorded at admission and on each day. Day 1 was defined as the interval from admission to 8:00 AM on the next day; all other days were calendar days from 8:00 AM to 8:00 AM. The simplified acute physiology score (SAPS II)<sup>18,19</sup> at hospital admission was computed using the worst physical and laboratory data recorded during the first 24 h in the ICU. The SAPS II and logistic organ dysfunction (LOD) score<sup>18,19</sup> were computed daily. Duration of stays in the ICU and acute-care hospital and vital status at ICU and hospital discharge were recorded.

### Quality of the Database

Quality was checked in 2003 by reviewing a random 2% sample of the data recorded in each ICU. This was done by intensivists from other ICUs. Interrater correlation coefficients ranged from 0.67 to 1 for clinical variables and for severity and organ dysfunction scores;  $\kappa$  coefficients for qualitative variables ranged from 0.5 to 0.9.

### Criteria for VAP

Suspected VAP was defined as the development of persistent pulmonary infiltrates shown on the chest radiograph in combination with purulent tracheal secretions and/or body temperature  $\geq 38.5^\circ\text{C}$  or  $\leq 36.5^\circ\text{C}$ , and/or peripheral blood leukocyte count  $\geq 10 \times 10^9/\text{L}$  or  $\leq 4 \times 10^9/\text{L}$ . All patients with suspected VAP underwent fiberoptic bronchoscopy with protected specimen brush and/or BAL or single-sheathed blind plugged telescopic catheter specimen collection before receiving antimicrobial therapy. Confirmed early onset pneumonia was defined as a positive protected specimen brush result ( $\geq 10^3$  cfu/mL), a positive plugged telescopic catheter result ( $\geq 10^3$  cfu/mL), or a positive BAL fluid result ( $\geq 10^4$  cfu/mL).

### Exposed Patients and Matching of Unexposed Patients

An exposed patient was defined as having Candida colonization of the respiratory tract while receiving MV. Unexposed patients did not have Candida colonization of the respiratory tract. They were matched to exposed patients on year of admission and centers. In addition, an unexposed patient had to have MV duration at least as long as the precolonization MV duration in the exposed patient. Matching was done using a macro procedure with statistical software (SAS Institute; Cary, NC) [<http://www.outcomerea.org/ehmt/matchmacro.pdf>].

### Statistical Analysis

The characteristics of patients with and without respiratory Candida colonization were described using the median and quartiles for continuous variables. To determine the incidence of respiratory Candida colonization, we used the Kaplan-Meier method.

The increase in the risk of VAP was assessed by conditional logistic regression analysis for 1:n matching, using the SAS procedure (PHREG, Version 8.02; SAS Institute) in a nested exposed-unexposed design. An exposed patient was a patient free from VAP at Candida colonization time. An unexposed patient

was a patient with VAP before colonization time or without Candida colonization. In the exposed patients, only VAP cases occurring at least two days after the onset of bronchial Candida colonization were considered. Similar exposed-unexposed selections were performed using *P. aeruginosa* VAP and *Staphylococcus aureus* VAP as events of interest. Patients were considered between MV onset and occurrence of VAP, ICU discharge, or death.

We calculated crude odds ratio (OR) and OR adjusted on matching criteria and variables unbalanced between exposed and unexposed patients. Analyses were adjusted on patient characteristics (direct admission, age, sex, SAPS II, LOD, presence or absence of any chronic illness [binary variable], infection or acute lung injury at ICU admission, use of vasopressors, hemodialysis or hemofiltration, sucralfate, antimicrobials agents including antifungal agents).

Results were expressed as OR and 95% confidence interval (CI). All statistical tests were two tailed, and  $p < 5\%$  was considered significant. All statistical analysis was performed using statistical software (version 8.02; SAS Institute).

## RESULTS

During the 4-year study period, 803 immunocompetent patients received MV for  $> 2$  days in the six study ICUs. Among them, 214 patients (26.6%) had respiratory tract Candida colonization. Patient characteristics are reported in Table 1, and the patient flowchart is shown in Figure 1. Thirty patients had colonization before MV onset. The Candida colonization rate was 19.54% (16.48–22.60) on day 5, 31.49% (27.10–35.88) on day 15, and 33.66% (28.76–38.56) on day 30. *C. albicans* was the main species (67.7%), followed by *Candida glabrata* (20%) and *Candida tropicalis* (13%). Each of these three species was usually the only pathogen retrieved from the respiratory tract, whereas *Candida krusei*, *Candida parapsilosis*, and *Candida lusitanae* were generally found in combination with another Candida species. Of the 386 patients who were selected according to the nested exposed/unexposed analysis (model 1), extrapulmonary Candida colonization was found in 85 patients (39.7%) with respiratory tract Candida colonization but in only 49 unexposed patients (8.3%). Moreover, extrapulmonary Candida colonization was more common and more extensive in exposed than in unexposed patients. As shown in Table 1, exposed patients were older, had a higher LOD score at ICU admission, were more frequently admitted for acute respiratory failure or infection and less frequently for coma, and were more likely to have received antibiotics within the first 3 days in the ICU. Antifungal therapy was prescribed more frequently in patients with respiratory tract Candida colonization than in other patients (7.5% vs 2.9%,  $p = 0.0038$ ).

As shown in Table 1, respiratory tract Candida colonization was associated with a longer time on MV and longer durations of ICU and hospital stays.

**Table 1—Patient Characteristics\***

Characteristics	Respiratory Tract Candida Colonization (n = 214)	No Respiratory Tract Candida Colonization (n = 589)	p Value†
Patient age, yr			
< 54	52 (24.3)	213 (36.2)	0.002
54 to 77	116 (54.2)	294 (49.9)	0.3
> 77	46 (21.5)	82 (19.9)	0.01
Diabetes mellitus	10 (4.7)	14 (2.4)	0.1
Reasons for ICU admission			
Acute respiratory failure	71 (33.2)	129 (21.9)	0.0011
Shock	55 (25.7)	142 (24.1)	0.6
Coma	33 (15.4)	199 (33.8)	< 0.0001
Infection at admission	114 (53.3)	204 (34.6)	< 0.0001
Direct admission	80 (37.4)	334 (46.7)	< 0.0001
SAPS II score at admission (range)	45 (33–60)	47 (36–61)	0.2
LOD score at admission (range)	5 (3–7)	6 (3–8)	0.038
Acute lung injury at admission‡	150 (71.1)	365 (63.5)	0.047
ARDS at admission§	89 (42.2)	222 (38.6)	0.44
Need for vasopressors	144 (67.3)	340 (57.7)	0.014
Antibiotics within 3 d after ICU admission	176 (82.2)	429 (72.8)	0.0062
Type of antibiotics			
Anti-Pseudomonas drugs (ceftazidime and imipenem)	25 (11.7)	38 (6.4)	0.015
Aminoglycosides			
Glycopeptides	33 (15.4)	53 (9)	0.009
Quinolones	27 (12.7)	37 (6.3)	0.003
Ureido-penicillin	49 (22.9)	78 (13.2)	0.0009
Antifungal agents	16 (7.5)	17 (2.9)	0.0038
Duration of MV (range), d	13 (7–24)	6 (3–12)	< 0.0001
Duration of MV/ICU length of stay (range), d	82 (67–97)	75 (58–96)	0.008
Occurrence of VAP	51 (23.8)	114 (19.3)	0.01
Occurrence of Pseudomonas VAP	19 (8.8)	30 (5)	0.1
Length of ICU stay (range), d	17 (9–32)	9 (5–17)	< 0.0001
Length of hospital stay (range), d	36 (19–74)	22 (9–45)	< 0.0001
Outcome			
ICU mortality	78 (36.4)	190 (32.3)	0.3
Hospital mortality	93 (43.5)	214 (36.3)	0.067

\*Data are presented as No. (%) unless otherwise indicated.

†Categorical variables were compared using the  $\chi^2$  test or Fisher exact test, as appropriate; and continuous variables were compared using the nonparametric Wilcoxon test.

‡Patients with PaO<sub>2</sub>/fraction of inspired oxygen ratio < 300 mm Hg.

§Patients with PaO<sub>2</sub>/fraction of inspired oxygen ratio < 200 mm Hg.

However, ICU and hospital mortality rates were not significantly different between patients with and without colonization. Candidemia occurred in six patients, including two patients (0.9%) with and four patients (0.7%) without respiratory tract Candida colonization.

In the matched exposed-unexposed (1:n) analysis, 191 colonized patients free from VAP at colonization time were the exposed patients. In the exposed patients, 46 acquired VAP (24.1%). In exposed patients, the mean time from onset of respiratory tract Candida colonization to VAP was 5 days (range, 2 to 7 days). The unexposed population consisted of 612 patients without Candida colonization before VAP. Three hundred eighty-six patients were selected according to the matching procedure; 68 patients (17.6%) had a VAP episode. The results of the matched exposed/unexposed nested cohort are re-

ported in Table 2. In a model comparing 191 exposed patients to 386 matched unexposed patients, the OR for VAP due to any organism was 1.55 (95% CI, 1.01 to 2.38; p = 0.047) but did not remain significant after careful adjustment. We found no significant association between respiratory-tract Candida colonization and *S aureus* VAP. On the contrary, we found an independent association between respiratory-tract Candida colonization and VAP was significant only for Pseudomonas (adjusted OR for Pseudomonas VAP, 2.22; 95% CI, 1.00 to 4.92; p = 0.049).

## DISCUSSION

In ICU patients receiving MV, Candida, a normal inhabitant of the oral cavity and GI tract, spreads

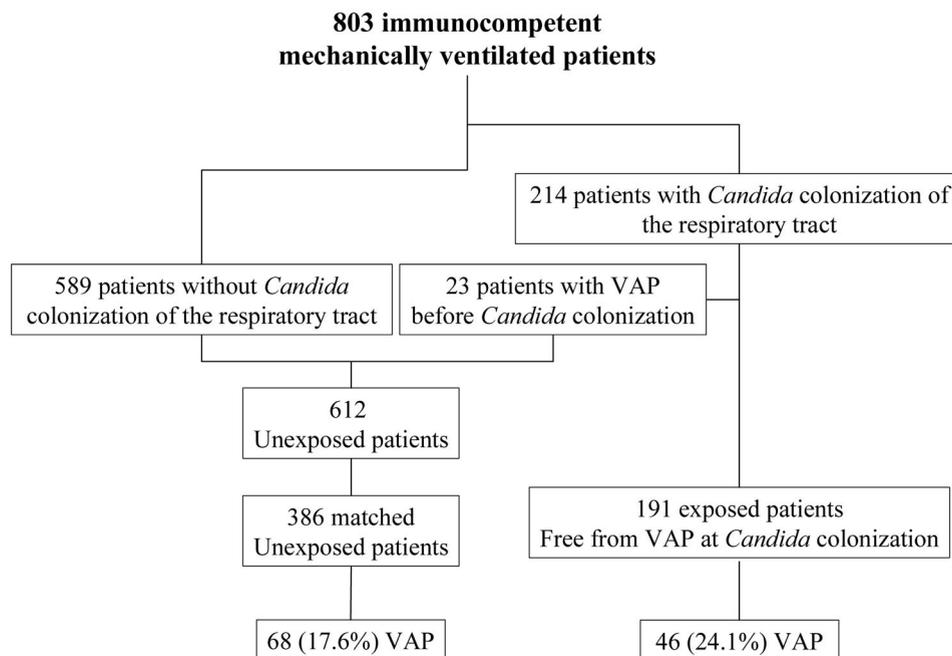


FIGURE 1. Patient flowchart.

along the respiratory tract down to the alveoli, so that endobronchial specimen findings are positive but no clinical or pathologic evidence of pneumonia is detectable.<sup>16,20</sup> In this situation, the positive specimens merely indicate colonization, and there is no

evidence of invasive pulmonary candidiasis (true candidal pneumonia), a condition related to haematogenous dissemination of *Candida* with selective tropism for the blood vessels and invasion of the lung parenchyma.<sup>2,3,21,22</sup> The multicenter study reported

**Table 2—Results of the Nested Exposed/Unexposed (1:n) Analysis\***

Models	Matching Variables	Pairs Successfully Matched, %	Outcome Variable of Interest	Patients, No.	Results, No.
1	Center; year of ICU admission; duration of MV greater or equal to time to occurrence of <i>Candida</i> colonization of the respiratory tract	100	VAP episodes	191 exposed; 386 unexposed	Exposed, 46 (24.1% of VAP); unexposed, 68 (17.1% of VAP); unadjusted OR, 1.55 (95% CI, 1.01 to 2.38; p = 0.047); adjusted OR, 1.58 (95% CI, 0.94 to 2.68; p = 0.086)
2	Center; year of ICU admission; duration of MV greater or equal to time to occurrence of <i>Candida</i> colonization of the respiratory tract	100	<i>P aeruginosa</i> VAP episodes	211 exposed; 394 unexposed	Exposed, 19 (9% of <i>P aeruginosa</i> VAP); unexposed, 19 (4.8% of <i>P aeruginosa</i> VAP); unadjusted OR, 1.99 (95% CI, 1.01 to 3.93; p = 0.047); adjusted OR, 2.22 (95% CI, 1.00 to 4.92; p = 0.049)
3	Center; year of ICU admission; duration of MV greater than or equal to time to occurrence of <i>Candida</i> colonization of the respiratory tract	100	<i>S aureus</i> VAP episodes	207 exposed; 398 unexposed	Exposed, 18 (8.7% of <i>S aureus</i> pneumonia); unexposed, 28 (7% of <i>S aureus</i> pneumonia); unadjusted OR, 1.38 (95% CI, 0.71 to 2.69; p = 0.3); adjusted OR, 1.27 (95% CI, 0.57 to 2.85; p = 0.6)

\*Analyses were adjusted on patient characteristics (direct admission, age, sex, SAPS II, LOD, presence of a chronic illness, infection or acute lung injury at ICU admission, use of vasopressors, hemodialysis or hemofiltration, sucralfate, antimicrobial agents).

here showed that *Candida* colonization of the respiratory tract was common, occurring in 25% of immunocompetent critically ill patients receiving MV. This is the first study that sought to identify diseases specifically related to *Candida* colonization of the respiratory tract. Although *Candida* colonization was not associated with increased mortality, longer durations were found for mean time receiving MV, mean time in the ICU, and mean time in the hospital. A finding from the present study is that in our selected patients, respiratory tract *Candida* colonization was associated with an increased risk for VAP and that this increase was explained by a greater risk of *Pseudomonas* VAP.

Interactions between bacteria and fungi have major environmental and medical consequences. Bacteria have been shown to induce morphologic changes in *Candida*,<sup>12</sup> and *Candida* morphology and virulence are significantly affected by the presence of *P aeruginosa*.<sup>11</sup> *Pseudomonas* produces a cell-cell signaling molecule (3-oxo-C12 homoserine lactone) capable of inhibiting *Candida* filamentation.<sup>11</sup> Moreover, Spinelli et al<sup>10</sup> showed that both *Candida* spp and *P aeruginosa* had the functional enzyme (2'-phosphotransferase) acting in concert with ligase to splice transfer RNA or other RNA molecules, a finding consistent with phylogenetic similarities between the two pathogens. In patients receiving MV, *Pseudomonas* forms a dense biofilm on *Candida*

filaments,<sup>8</sup> in agreement with the finding that *Candida* and *Pseudomonas* are among the most common pathogens retrieved from endotracheal tubes and from respiratory specimens in patients with VAP.<sup>1,7,8</sup>

In keeping with these data, our nested exposed/unexposed analysis found that *Candida* colonization of the respiratory tract was associated with an increased risk of VAP. A finding from our study was that this association was more pronounced for *Pseudomonas* VAP (9% vs 4.8%,  $p = 0.049$ ) than for other pathogens (Table 3). This finding, in addition with the above-described data supporting biological plausibility, suggests that respiratory-tract *Candida* colonization may be associated with an increased risk of *Pseudomonas* infection. To date, however, respiratory-tract *Candida* colonization is not recognized as requiring preemptive antifungal treatment. Moreover, the strength of the *Candida* colonization-*Pseudomonas* VAP association may be underestimated: in experimental or clinical models of concomitant infection with *C albicans* and *P aeruginosa*, *P aeruginosa* suppressed the growth of *C albicans in vitro*<sup>23,24</sup> and *in vivo*.<sup>25</sup>

Our study has several limitations. First, we considered that retrieval of *Candida* from the respiratory tract indicated colonization rather than infection. This position is based on our clinical experience and on the literature.<sup>2,3</sup> Furthermore, only a minority of our patients had evidence of invasive candidiasis or

**Table 3—Characteristics of the Patients in the Second Nested Exposed/Unexposed Analysis With *P aeruginosa* VAP Episodes as Outcome Measure\***

Characteristics	Respiratory Tract <i>Candida</i> Colonization (n = 211)	No Respiratory Tract <i>Candida</i> Colonization (n = 394)	p Value†
Patient age, yr	69 (55–76)	64 (50–74)	0.01
Reasons for ICU admission			
Acute respiratory failure	55 (26)	95 (24.1)	0.1
Shock	64 (30.3)	106 (26.9)	0.35
Coma	32 (15.2)	123 (31.2)	< 0.0001
Infection at admission	113 (53.6)	148 (37.5)	< 0.0001
Direct admission	69 (32.7)	205 (52)	< 0.0001
SAPS II score at admission (range)	45 (35–58.5)	48 (36–61)	0.33
LOD score at admission (range)	5 (3–7)	5 (3–8)	0.11
MV within 48 h	175 (82.9)	350 (89)	0.57
Acute lung injury at admission‡	156 (73.9)	257 (65.2)	0.22
ARDS at admission§	93 (44.1)	160 (40.6)	0.37
Need for vasopressors	147 (69.6)	245 (62.2)	0.10
Antibiotics within 3 d after ICU admission	166 (78.6)	303 (76.9)	0.27
Occurrence of VAP	48 (22.7)	69 (17.5)	0.07
Occurrence of <i>Pseudomonas</i> VAP	19 (9)	19 (4.8)	0.04

\*Data are presented as No. (%) unless otherwise indicated. Analyses were adjusted on patients characteristics (direct admission, age, sex, SAPS II, LOD, presence of a chronic illness, infection or acute lung injury at ICU admission, use of vasopressors, hemodialysis or hemofiltration, sucralfate, antimicrobial agents).

†Categorical variables were compared using the  $\chi^2$  test or Fisher exact test, as appropriate, and continuous variables using the nonparametric Wilcoxon test.

‡Patients with a PaO<sub>2</sub>/fraction of inspired oxygen ratio < 300 mm Hg.

§Patients with a PaO<sub>2</sub>/fraction of inspired oxygen ratio < 200 mm Hg.

candidemia. Second, our finding that *Candida* colonization of the respiratory tract was associated with extrapulmonary and multiple-site *Candida* colonization may indicate a need for a preemptive treatment, as previously suggested.<sup>5,26–28</sup> However, although antifungal prophylaxis has been successful in critically ill patients at high risk for candidemia,<sup>29,30</sup> no study has demonstrated benefits from preemptive antifungal therapy in critically ill patients with high *Candida* colonization index values.<sup>31</sup> A recent before/after intervention study from Piarroux et al<sup>32</sup> reported a reduced incidence of candidemia in critically ill surgical patients receiving preemptive antifungal therapy. However, no changes in ICU mortality rates could be observed. Third, although practices regarding the management of VAP and fungal infection and colonization were identical in the six participating ICUs, the study protocol did not include routine respiratory testing to look for *Candida* colonization, but only collection of bronchial specimens when VAP was suspected on clinical and biological grounds. Moreover, our patients might have had different number of cultures of respiratory specimen, a fact that may decrease the impact of the association reported. However, this means that our results reflect everyday practice and are easily applicable to critically ill patients receiving MV. Fourth, both *Candida* and *Pseudomonas* colonization might be consequences of previous antibiotic administration without significant association between these two pathogens. However, the lack of association with *Staphylococcus pneumoniae*, another consequence of antibiotics use, indicates that an association between *Candida* and *Pseudomonas* remains plausible.

This study demonstrates an association between *Candida* colonization of the respiratory tract and subsequent *Pseudomonas* VAP. A causal relationship is biologically plausible. Further studies should strive to determine whether decolonization of the respiratory tract using local or systemic antifungal therapy reduces the incidence of *Pseudomonas* VAP.

## APPENDIX

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