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

Elie Azoulay, MD, PhD; Jean-François Timsit, MD, PhD; Muriel Tafflet; Arnaud de Lassence, MD; Michael Darmon, MD; Jean-Ralph Zahar, MD; Christophe Adrie, MD, PhD; Maité Carroute-Orgeas, MD; Yves Cohen, MD; Bruno Mourvillier, MD; and Benoît Schlemmer, MD; for the Outcome Research Study Group†

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.¹ Clinical studies²,³ 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,²,³ 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. 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. 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 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). Moreover, El-Azizi et al 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 showed that recent Pseudomonas infection increased the risk of fatal candidiasis. Molecular studies identified phylogenetic similarities between the two pathogens, and Hogan et al 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. Antibiotic treatment of nosocomial pneumonia was in compliance with current guidelines. Invasive candidiasis was defined as recommended. 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.

**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; presence of diabetes mellitus (with the type and complications); admission category (medical, scheduled surgery, or unscheduled surgery);
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)\textsuperscript{18,19} at hospital admission was computed using the worse physical and laboratory data recorded during the first 24 h in the ICU. The SAPS II and logistic organ dysfunction (LOD) score\textsuperscript{18,19} 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 $\geq 38.5^\circ C$ or $\leq 36.5^\circ C$, and/or peripheral blood leukocyte count $\geq 10 \times 10^9/L$ or $\leq 4 \times 10^9/L$. 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 ($\geq 10^5$ cfu/mL), a positive telescopic catheter specimen 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/ehtm/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 $p < 0.05$ 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 lusitaniae* 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.
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, 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 reported 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...
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.\textsuperscript{16,20} 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 hematogenous dissemination of Candida with selective tropism for the blood vessels and invasion of the lung parenchyma.\textsuperscript{2,3,21,22} The multicenter study reported

**Table 2—Results of the Nested Exposed/Unexposed (1:n) Analysis*\textsuperscript{16,20}**

<table>
<thead>
<tr>
<th>Models</th>
<th>Matching Variables</th>
<th>Pairs Successfully Matched, %</th>
<th>Outcome Variable of Interest</th>
<th>Patients, No.</th>
<th>Results, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Center; year of ICU admission; duration of MV greater or equal to time to occurrence of Candida colonization of the respiratory tract</td>
<td>100</td>
<td>VAP episodes</td>
<td>191 exposed; 386 unexposed</td>
<td>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)</td>
</tr>
<tr>
<td>2</td>
<td>Center; year of ICU admission; duration of MV greater or equal to time to occurrence of Candida colonization of the respiratory tract</td>
<td>100</td>
<td><em>P. aeruginosa</em> VAP episodes</td>
<td>211 exposed; 394 unexposed</td>
<td>Exposed, 19 (9%) of <em>P. aeruginosa</em> VAP; unexposed, 19 (4.8%) of <em>P. aeruginosa</em> 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)</td>
</tr>
<tr>
<td>3</td>
<td>Center; year of ICU admission; duration of MV greater than or equal to time to occurrence of Candida colonization of the respiratory tract</td>
<td>100</td>
<td><em>S. aureus</em> VAP episodes</td>
<td>207 exposed; 398 unexposed</td>
<td>Exposed, 18 (8.7%) of <em>S. aureus</em> pneumonia; unexposed, 28 (7%) of <em>S. aureus</em> 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)</td>
</tr>
</tbody>
</table>

*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, and Candida morphology and virulence are significantly affected by the presence of P aeruginosa. Pseudomonas produces a cell-cell signaling molecule (3-oxo-C12 homoserine lactone) capable of inhibiting Candida filamentation. Moreover, Spinelli et al 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, 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.

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 and in vivo.

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. 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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Respiratory Tract Candida Colonization (n = 211)</th>
<th>No Respiratory Tract Candida Colonization (n = 394)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age, yr</td>
<td>69 (55–76)</td>
<td>64 (50–74)</td>
<td>0.01</td>
</tr>
<tr>
<td>Reasons for ICU admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>55 (26)</td>
<td>95 (24.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>Shock</td>
<td>64 (30.3)</td>
<td>106 (26.9)</td>
<td>0.35</td>
</tr>
<tr>
<td>Coma</td>
<td>32 (15.2)</td>
<td>123 (31.2)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Infection at admission</td>
<td>113 (53.6)</td>
<td>148 (37.5)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Direct admission</td>
<td>69 (32.7)</td>
<td>205 (52)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>SAPS II score at admission (range)</td>
<td>45 (35–58.5)</td>
<td>48 (36–61)</td>
<td>0.33</td>
</tr>
<tr>
<td>LOD score at admission (range)</td>
<td>5 (3–7)</td>
<td>5 (3–8)</td>
<td>0.11</td>
</tr>
<tr>
<td>MV within 48 h</td>
<td>175 (82.9)</td>
<td>350 (89)</td>
<td>0.57</td>
</tr>
<tr>
<td>Acute lung injury at admission†</td>
<td>156 (73.9)</td>
<td>257 (65.2)</td>
<td>0.22</td>
</tr>
<tr>
<td>ARDS at admission‡</td>
<td>93 (44.1)</td>
<td>160 (40.6)</td>
<td>0.37</td>
</tr>
<tr>
<td>Need for vasopressors</td>
<td>147 (69.6)</td>
<td>245 (62.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Antibiotics within 3 d after ICU admission</td>
<td>166 (75.6)</td>
<td>303 (76.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>Occurrence of VAP</td>
<td>48 (22.7)</td>
<td>69 (17.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Occurrence of Pseudomonas VAP</td>
<td>19 (9)</td>
<td>19 (4.8)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*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 χ² test or Fisher exact test, as appropriate, and continuous variables using the nonparametric Wilcoxon test.
‡Patients with a PaO₂/fraction of inspired oxygen ratio < 300 mm Hg.
§Patients with a PaO₂/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.\textsuperscript{5,26–28} However, although antifungal prophylaxis has been successful in critically ill patients at high risk for candidemia,\textsuperscript{29,30} no study has demonstrated benefits from preemptive antifungal therapy in critically ill patients with high Candida colonization index values.\textsuperscript{31} A recent before/after intervention study from Piarroux et al\textsuperscript{32} reported a reduced incidence of candidemia in critically ill surgical patents 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 pneumonia, 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.

\textbf{APPENDIX}

\textit{Members of the Outcomerea Study Group}

\textbf{Scientific Committee:} Timsit, Jean-François, MD, PhD, Staff Physician, ICU, CHU Grenoble, France; Troché, Gilles, MD, Staff Physician, Hôpital A. Becleère, Clamart France; Moine, Pierre, MD, PhD, Staff Physician, DAR, Hôpital Lariboisière, Paris, France; De Lassence, Arnaud, MD, Staff Physician, ICU, Hôpital Louis Mourier, Colombes, France; Azoulay, Elie, MD, PhD, Staff Physician, ICU, Hôpital Saint Louis, Paris, France; Cohen, Yves, MD, Professor, ICU, Hôpital Avicenne, Bobigny, France; Garrouste-Orgeas, Maïté, MD, Staff Physician, ICU, Hôpital Saint Joseph, Paris, France; Fosse, Jean-Philippe, MD, Staff Physician, ICU, Hôpital Avicenne, Bobigny, France; Soufir, Lilia, MD, Staff Physician, ICU, Hôpital Saint Joseph, Paris, France; Zahar, Jean-Ralph, MD, Attending Physician, Microbiology Department, Hôpital Necker, Paris, France; Adrie, Christophe, MD, Staff Physician, ICU, Hôpital Delafontaine, Saint Denis, France; Carlet, Jean, MD, Staff Physician, ICU, Hôpital Saint Joseph, Paris, France; L’Hérétie, François, MD, Attending Physician, ICU, Hôpital Bichat, Paris, France.

\textbf{Biostatistical and Informatics Expertise:} Chevret, Sylvie, MD, PhD, Professor, Medical Computer Sciences and Biostatistics Department, Hôpital Saint Louis, Paris, France; Alberti, Corinne, MD, Staff Physician, Medical Computer Sciences and Biostatistic Department, Hôpital Saint Louis, Paris, France; Lecorre, Frederik, Informatician, Supélec, France; Nakache, Didier, Informatic Engineer, Conservatoire National des Arts et Métiers, Paris, France; Tafflet, Muriel, Biostatistical Engineer, Outcomerea Organization, France.

\textbf{Investigators of the Outcomerea Database:} Bornstain, Caroline, MD, Staff Physician, ICU, Hôpital Européen Georges Pompidou, Paris, France; Thuong, Marie, MD, Staff Physician, ICU, Hôpital Delafontaine, Saint Denis, France; Costa de Beauregard, Marie-Allelète, MD, Staff Physician, Nephrology, Hôpital Tenon, Paris, France; Colin, Jean-Pierre, MD, Staff Physician, ICU, Hôpital de Dourdan, Dourdan, France; Le Miere, Eric, MD, Attending Physician, ICU, Hôpital Louis Mourier, Colombes, France; Caubel, Antoine, MD, Attending Physician, ICU, Hôpital Saint Joseph, Paris, France; Marie, William, MD, Attending Physician, ICU, Hôpital Saint Joseph, Paris, France; Cheval, Christine, MD, Staff Physician, SICU, Hôpital Saint Joseph, Paris, France; Vantalon, Eric, MD, Staff Physician, SICU, Hôpital Saint Joseph, Paris, France; Clec’h Christophe, MD, Staff Physician, ICU, Hôpital Avicenne, Bobigny, France; Vincent, François, MD, Staff Physician, Nephrology, Hôpital Tenon, Paris, France; Salah, Amar, MD, Staff Physician, ICU, Hôpital Louis Mourier, Colombes, France; Montesino, Laurent, MD, Attending Physician, ICU, Hôpital Bichat, Paris, France; Pigué, Etienne, MD, Staff Physician, ICU, Hôpital Louis Mourier, Colombes, France; Boyer, Alexandre, MD, Staff Physician, ICU, Hôpital Pellegrin, Bordeaux, France; Mourvillier, Bruno, MD, Staff Physician, ICU, Hôpital d’Aulnay ss bois, France; Jamali, Samir, MD, Staff Physician, ICU, Hôpital de Dourdan, Dourdan, France; Moreau, Delphine, MD, Staff Physician, ICU, Hôpital Saint Louis, Paris, France; Magali, Ciroldi, MD, Staff Physician, ICU, Hôpital Saint Louis, Paris, France; Duguet, Alexandre, MD, Attending Physician, Hôpital Pitié-Salpêtrière, Paris, France; Laplace, Christian, MD, Attending Physician, ICU, Hôpital Kremlin-Bicêtre, Bicêtre, France; Lazard, Thierry, MD, Staff Physician, ICU, Hôpital de la Croix St Simon, Paris, France; Schwebel, Carole, MD, Attending Physician, ICU, Hôpital Michallon, Grenoble, France; Lessire, Henri, MD, Attending Physician, ICU, Hôpital Michallon, Grenoble, France.

\textbf{References}


9 Neely AN, Law EJ, Holder IA. Increased susceptibility to lethal Candida infections in burned mice preinfected with Pseudomonas aeruginosa or pretreated with proteolytic enzymes. Infect Immun 1986; 52:200–204