The diagnosis of ventilator-associated pneumonia (VAP) is often difficult because many other conditions can produce sepsis and new lung infiltrates in critically ill patients. Significant numbers of a nosocomial pathogen in quantitative cultures of bronchial specimens convert a suspicion of VAP to a near certainty. A protected-specimen brush (PSB) culture showing at least $10^3$ cfu/mL, a positive result of a BAL fluid smear, or a BAL fluid culture with at least $10^4$ cfu/mL is specific for VAP in patients without recent changes in antimicrobial therapy. The organisms most often responsible for VAP are methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and Enterobacteriaceae. In early-onset VAP, *Streptococ-
cus pneumoniae, Haemophilus influenzae, and methicillin-sensitive S aureus are causative pathogens.

Significant growth of oropharyngeal or cutaneous commensal microorganisms (OCCs) in quantitative cultures of distal bronchial specimens are more difficult to interpret. Because their virulence is low, OCCs are widely believed to be nonpathogenic.4 The presence in distal bronchial specimens of microorganisms such as Neisseria spp, Corynebacterium spp, or coagulase-negative Staphylococcus (CGNS) is often considered to indicate lung colonization or specimen contamination.

However, there is ample evidence that these same species can produce various infections in both immunocompetent and immuno compromised hosts.5–10 Numerous studies11,12 have shown that critically ill patients have complex deficiencies in both cellular and humoral immunity. Moreover, OCCs have been found in lung cultures in postmortem studies.13,14 These data may prompt ICU physicians to treat patients with OCCs in distal bronchial specimens.

Most studies investigating the potential role of OCCs as lung pathogens15–21 have reported the rate of OCC recovery in series of patients with VAP. The meaning of significant growth in quantitative cultures of OCCs has been neither investigated in depth nor discussed in reviews or consensus conferences about VAP.22,23

To evaluate the meaning of OCC-positive quantitative distal bronchial cultures in patients with suspected VAP, we retrospectively reviewed the records of patients with VAP included in the database of our ICU. We identified those patients in whom only one or more OCCs were found in significant concentrations in distal bronchial cultures (OCC-VAP). We evaluated the degree of confidence with which experts diagnosed VAP caused by OCCs in these patients, and we conducted an exposed/unexposed study to look for organ dysfunction and/or excess mortality associated with OCC-VAP.

**MATERIALS AND METHODS**

**Study Population**

For the last 10 years, all patients with nosocomial infections seen in our ICU have been prospectively recorded in a computer database. Our 10-bed polyvalent ICU is in a 465-bed teaching hospital that serves both as a referral center and as a primary care center. VAP prophylaxis was carried out in compliance with the guidelines of the Comité Technique des Infections Nosocomiales.24 In particular, endotracheal suctioning was performed at 3-h intervals at a pressure of < ~80 cm H2O using a sterile disposable catheter that was handled with sterile compresses and nonsterile gloves by nurses who washed their hands before and after the procedure.

We reviewed all VAP episodes recorded between August 1, 1990, and August 1, 2000, and selected the records of patients with significant growth in quantitative cultures of distal bronchial specimens of OCCs only. We excluded patients with AIDS, neutropenia (i.e., < 500 neutrophils/µL), hematologic malignancies, or a change in antimicrobial therapy within 3 days before the bronchoscopy that provided the diagnosis of VAP. For each case of VAP, we recorded body temperature, peripheral leukocyte count, the presence of a purulent tracheal aspirate, and the presence of a new chest radiograph infiltrate within 48 h before the bronchoscopy. A clinical pulmonary infection score (CPIS) was calculated for each patient.25

**Definitions and Diagnosis of OCC-VAP**

VAP was defined as any lower respiratory tract infection that developed ≥ 48 h after ICU admission in patients receiving invasive mechanical ventilation (IMV). A clinical suspicion of pneumonia was defined as the presence of a new or persistent lung density seen on chest radiographs with one or more of the following conditions: temperature of > 38.5°C or < 36.5°C; peripheral leukocyte count of > 11,000 cells/µL or < 5,000 cells/µL; and the presence of purulent endotracheal aspirate. All patients with clinically suspected pneumonia underwent fiberoptic bronchoscopy with PSB sampling and BAL before any change in antibiotic therapy was made. Specimens were collected and processed as described elsewhere.26 The study team was very familiar with these techniques, which have not been changed in the last 10 years. VAP was diagnosed if the PSB specimen yielded ≥ 107 cfu/mL and/or the BAL fluid yielded ≥ 104 cfu/mL. Legionella pneumonia was diagnosed based on a positive result of a qualitative culture, urinary antigen test, or serum antibody test for the organism. Chlamydia spp and Mycoplasma spp were tested for in a few patients, none of whom had positive results.

OCC-VAP was defined as the presence of VAP with significant growth in quantitative cultures of OCCs only. The organisms were as follows: Streptococcus spp other than β-hemolytic streptococci (groups A, C, and G, and S pneumoniae); Neisseria spp; Moraxella catarrhalis; Corynebacterium spp; Haemophilus spp other than H influenzae; and CGNS other than Staphylococcus lugdunensis. Cases of VAP with the growth of one or more OCCs and at least one organism known to be pathogenic were excluded.

**Differential Diagnosis**

Patients with suspected VAP were routinely screened for other causes of lung density and fever. The definitions of these causes were adapted from Meduri et al27 and are listed below.

1. Atelectasis: resolution of pulmonary densities within 48 h of bronchoscopy without antibiotic therapy;
2. Congestive heart failure: hemodynamic evidence of increased pulmonary artery occlusion pressure or resolution of pulmonary densities within 48 h after bronchoscopy and after diuretic therapy initiation;
3. Deep venous thrombosis: positive Doppler ultrasound findings in the lower limb veins followed by treatment with anticoagulant agents;
4. Pulmonary embolism: suggestive findings on a ventilation-perfusion scintigram or angio-CT lung scan followed by anticoagulant therapy;
5. Drug fever: resolution of fever with drug withdrawal and recurrence of fever with the administration of a drug of the same class;
6. Surgical site infection: discharge of pus from a surgical wound.
Medical Record Review by Senior Physicians

Each case was independently and blindly reviewed by three senior physicians with extensive experience in the management of VAP. Each of these experts was asked to answer the following five questions: (1) Do you believe the prebronchoscopy findings indicate a suspicion of VAP? (2a) How confident are you that your previous answer is correct (on a four-item verbal scale, from limited confidence to complete confidence)? (2) Do you believe that the findings, including the microbiological results, indicate a diagnosis of VAP? (2a) How confident are you that your previous answer is correct (same scale as in question 1a)? and (3) Would you have given antibiotics selected for activity against one or more OCCs? To agree or to reject the possible VAP diagnosis, experts used arguments adapted from a previous report from our team, which were based on the recovery of the patient with or without effective antimicrobial therapy and on a proven or suspected alternate diagnosis.

Data Analysis

To find out whether OCC-VAP was associated with increased illness severity, we determined the logistic organ dysfunction (LOD) score27 at ICU admission, 3 days before undergoing the bronchoscopy (D3), and on the day of the bronchoscopy (D0). We estimated the risk of mortality related to OCC-VAP in an exposed/unexposed analysis. Unexposed patients were defined as patients in whom VAP had neither been diagnosed nor suspected.

Assuming a 35% mortality rate in non-VAP patients (ie, patients receiving IMV but free of VAP), and given that only 28 patients had OCC-VAP, two no-VAP patients per OCC-VAP patient were needed to detect a twofold mortality increase in OCC-VAP patients, with a power of 80% and a type I error rate of 5%. A list of no-VAP patients was retrieved from the database. Each OCC-VAP patient was matched with two no-VAP patients on the following characteristics: calendar period of ICU hospitalization; IMV duration (required, in no-VAP patients, to be at least equal to that in the corresponding OCC-VAP patient before the day they underwent the bronchoscopy); predicted mortality as assessed by simplified acute physiology score (SAPS) II score at ICU admission (± 10%); and sex. Appropriate no-VAP patients were identified by reviewing the database records of all patients admitted to the ICU during the study period, except for those with OCC-VAP. A software macro (SAS: SAS Institute; Cary, NC) was used to select no-VAP patients without input from the investigators. The medical records of no-VAP patients were reviewed to calculate the LOD score at ICU admission, LOD score after the ICU stay duration at which the matched OCC-VAP patient underwent bronchoscopy (LOD-D0); ie, when the IMV duration was equal to that in the matched OCC-VAP patient), and 3 days before D0 (ie, LOD-D3).

Statistical Analysis

Patient characteristics are presented as the mean ± SD or No. (percentages). Two-way analysis of variance on ranks were used for continuous data and a two-covariates logistic model for qualitative data (in both cases, one factor was exposure and the other was the triplet formed by each OCC-VAP patient and the two matched no-VAP patients). Survival in OCC-VAP and no-VAP patients was compared using conditional logistic regression. A Wilcoxon test for paired data was done to compare LOD scores before and at the time of OCC-VAP. All statistical tests were run by a statistical software package (SAS, version 6.12; SAS Institute). All tests were two-sided, and p values ≤ 0.05 were considered to be statistically significant.

RESULTS

VAP Patients

Three thousand five hundred fifty-four patients were admitted to our ICU during the 10-year study period. Of these, 1,955 patients (55%) received IMV, and 292 patients had 369 episodes of VAP. There were 77 episodes of polymicrobial pneumonia with the significant growth of one or more classic nosocomial pathogens and one or more OCCs. These cases were not included in the OCC-VAP category. Thirty-three episodes of OCC-VAP occurred in 32 patients, accounting for 9% of all VAP cases (33 of 369 cases). The overall rate of occurrence of OCC-VAP was 0.9 per 1,000 patients admitted to the ICU. Four OCC-VAP episodes in four patients were excluded because of incomplete data (n = 2) or because the patients had AIDS (n = 2). This left 29 OCC-VAP episodes in 28 patients (16 men and 12 women) who had a mean age of 68 ± 10 years (age range, 34 to 82 years). Twenty-five patients had chronic conditions including the following: heart failure (6 patients); COPD (5 patients, including one receiving long-term oral glucocorticoid therapy of < 0.5 mg/kg/d); vasculitis (caused by rheumatoid arthritis in two patients, Wegener granulomatosis in one patient, and giant cell arteritis in one patient) requiring glucocorticoid therapy of > 0.5 mg/kg/d and/or immunosuppressive therapy (ie, cyclophos-
phamid or methotrexate); diabetes mellitus (four patients) or a solid malignancy treated without chemotherapy (six patients).

All 25 patients received IMV for a mean duration of 23 ± 20 days. Ten cases of OCC-VAP occurred before the sixth ICU day, and 19 cases occurred beyond the sixth ICU day. Of the 29 episodes of OCC-VAP, 10 occurred within the first 5 days of the patient receiving IMV.

All 29 OCC-VAP episodes were characterized by a new chest infiltrate, 26 by a purulent tracheal aspirate, 23 by a fever of 38.5°C, and 18 by a leukocyte count of >11,000 cells/μL. Two, three, or four of these symptoms were present in 29, 17, and 8 episodes, respectively. The mean CPIS was 7.6 ± 1.95, and the median CPIS was 8. The CPIS was >6 in 20 cases. Bacteriologic data are shown in Table 1. Both PSB sampling and BAL were performed in 22 episodes. In eight episodes, both the PSB and the BAL fluid cultures were positive and the BAL fluid smear showed >5% intracellular organisms (ICOs); in five episodes, both cultures were positive but the BAL fluid smear showed <5% ICOs; in four episodes, either the PSB specimen or the BAL fluid culture was positive with >5% ICOs; and in 12 episodes, either the PSB or the BAL fluid culture was positive and <5% ICOs were observed. In two patients, an autopsy performed within 3 days after the bronchoscopy showed histologic evidence of pneumonia. In the patient in whom the lung was cultured, no OCCs were recovered, but effective antibiotic therapy was given between the time that the patient underwent bronchoscopy and death. In the three other patients who had OCC-VAP with the presence of CGNS, a CT scan showed lung abscesses.

Forty-seven OCCs were recovered during the 29 episodes of OCC-VAP, 34 in concentrations above the cutoffs defining positive quantitative cultures (Table 2). In 10 episodes, more than one OCC was recovered, and 9 of these 10 episodes occurred within 8 days after intubation. The mean bacterial index was 5.8 (median, 5; SD, 2.7) for the 29 episodes and 8.3 ± 2.8 for the 10 polymicrobial episodes.

In six episodes with CGNS, no other organisms were found. Streptococcus epidermidis was involved in five cases. The numbers of patients with two, three, or four criteria for a clinical suspicion of VAP were two, three, and one, respectively. One of these six episodes occurred in a patient receiving glucocorticoid therapy, >1 mg/kg, and methotrexate therapy for rheumatoid arthritis. Five episodes occurred >5 days after intubation. Only in two episodes did the BAL fluid smear show >2% ICOs, and although all PSB cultures were positive, only two episodes had BAL fluid cultures with >10⁴ cfu/mL. In three episodes, community-acquired pneumonia had been the reason for ICU admission and was a possible cause for the lung infiltrate, heart failure was present in two other episodes, whereas in the remaining episode there was no alternative diagnosis. Lung abscesses were demonstrated by CT scans in two patients who had VAP with *S epidermidis*. Three of these six patients received antibiotics that were active against the recovered OCCs. One patient died of a cause considered to be unrelated to OCC-VAP.

Nine of the 11 strains of CGNS recovered in the study were resistant to mexitcin and fluoroquinolones, and 8 strains were resistant to gentamicin. The minimum inhibitory concentration (MIC) of vancomycin was always <8 μg/mL. Except for a *Streptococcus oralis* isolate with a high amoxicillin MIC (4 mg/mL) that was responsible for a lack of response to antibiotic therapy, all the Streptococcus strains were sensitive to amoxicillin. All Gram-negative rods were sensitive to third-generation cephalosporins or co-amoxiclav (one strain of *M catarrhalis* and two strains of *Haemophilus parainfluenzae* produced a β-lactamase).

The possible causes for disagreement between experts are shown in Table 1. Twenty-three alternative causes of new radiologic infiltrates were found in 17 episodes, and 28 alternative causes of fever were found in 20 episodes. In 11 episodes, there was an alternative explanation to both the fever and the new radiologic infiltrate. Only in four episodes was there no alternative diagnosis for the fever or new radiologic infiltrate.

The physicians in charge of the patients decided to treat 22 episodes, although the antimicrobial agents used were active against the OCCs in only 20 episodes. Of the seven patients who were not treated for the bronchoscopy findings, two had another infection for which they received antibiotics that were active against the bronchial OCCs. Ten of the 28 patients died. An autopsy was performed in five patients. In two of these five patients, histologic evidence of pneumonia was found. In the three other patients, death occurred later, after the resolution of the VAP.

Therefore, five patients did not receive an antimicrobial agent and two others received inadequate antimicrobial therapy. Among these seven patients, three died and lung abscesses were diagnosed in two. An 80-year-old woman (Table 1, case 4) had a community-acquired pneumococcal pneumonia with shock and acute renal failure; 16 days later, VAP was suspected and methicillin-resistant *S epidermidis* found in PSB specimen and BAL fluid. She re-
received a 48-h course of a third-generation cephalosporin, developed a lung abscess 1 week later, and died from multiple organ failure 14 days after the occurrence of OCC-VAP. No autopsy was performed. A 44-year-old man (Table 1, case 17) was admitted to the ICU for meningoencephalitis, had
S. oralis isolated in PSB specimens and BAL fluid 15 days later, and was treated with amoxicillin. Unfortunately, the streptococcal strain had a reduced sensitivity to amoxicillin (MIC, 4 μg/mL) and was still isolated 6 days later in specimens from a PSB procedure and in fluid from BAL, which had been performed because of insufficient or poor improvement. Cefotaxime was prescribed. The patient died 2 months after the ICU admission from multiple organ failure in the setting of Pseudomonas bacteremia. A 70-year-old woman (Table 1, case 27) was admitted to the ICU for acute respiratory failure 1 week after undergoing a pneumonectomy procedure for lung cancer. A bronchoscopy was performed on the day of ICU admission, but no antibiotic therapy was prescribed. A pulmonary embolism was suspected, shock developed, and the patient died the next day. S. oralis and Streptococcus sanguis were isolated from the BAL fluid. An autopsy showed histologic findings of pneumonia without pulmonary emboli. The four other patients survived (Table 1, cases 5, 9, 13, and 22), but three patients had different differential diagnoses (heart failure, two patients; atelectasis, one patient). The last patient, admitted to the ICU for inhalation pneumonia, developed a lung abscess after receiving 10 days of mechanical ventilation. S. epidermidis was recovered from BAL fluid and PSB specimens. The abscess was drained, but the pus was sterile.

The three experts who reviewed the 29 episodes agreed, before reading the PSB specimen and BAL fluid test results, that VAP was a possibility in 12 episodes but could be ruled out in 4 others. In these 16 episodes, confidence with the diagnosis was almost complete or was complete in 44% and 14% of episodes, respectively. Concerning the PSB and BAL findings, the three experts agreed on 23 episodes (VAP caused by OCCs, 14 episodes; no-VAP caused by OCCs, 9 episodes). Confidence was almost complete and was complete in 44% and 25% of episodes, respectively. The patients in whom the 14 episodes occurred that were considered by all three senior physicians to be VAP caused by OCCs were treated with antibiotics, which were ineffective for the recovered microorganisms in one episode. All three experts agreed that treatment was necessary in 16 episodes and were unnecessary in 7 episodes. The data on the disagreement among are reported in Table 1. The main reason for disagreement among the experts was the relevance of a potential differential diagnosis. A description of patient subsets is provided in Table 1. All three episodes caused by H. parainfluenzae only and three of four episodes caused by M. catarrhalis only were categorized by all three physicians as VAP caused by OCCs. In contrast, in none of the episodes with CGNS only did all three physicians agree on a diagnosis of VAP caused by OCCs. The mean number of ICOs in BAL fluid smears was significantly different in episodes for which all three experts gave a diagnosis of VAP caused by OCC than in the other episodes.

OCC-VAP/No-VAP Study

The development of OCC-VAP was associated with a significant increase in disease severity, as assessed by the LOD score (LOD-3D, 3.8 ± 2.5; LOD-D0, 5.9 ± 2.7; p = 0.018). During the corresponding hospitalization days, no significant increase was found in the no-VAP group.

No-VAP patients were matched to OCC-VAP patients by SAPS II score at ICU admission and by IMV duration (which had to be as long or longer as in the OCC-VAP patient) [Table 4]. Matching was always successful for SAPS II score and IMV duration. The crude in-ICU death rate was 36% (10 of 29 patients) among the OCC-VAP patients and 36% (20 of 58 patients) among the no-VAP patients. We found no differences between OCC-VAP and no-VAP patients, except for the LOD score on the day of OCC-VAP (or on the corresponding day in the matched no-VAP patient). OCC-VAP was not associated with excess mortality in the OCC-VAP/no-VAP study (odds ratio [OR], 1.19; 95% confidence interval [CI], 0.41 to 1.72; p = 0.75) even after further adjustment on the LOD score 3 days earlier (OR, 1.19; 95% CI, 0.41 to 3.46; p = 0.8). The mean ICU stay was 6 days longer in the OCC-VAP patients than in the no-VAP patients.

**Discussion**

We are not aware of earlier studies specifically designed to investigate the role for OCCs in the pathogenesis of VAP. However, OCCs accounted for 9% of VAP episodes that were recorded in our 10-year database and have been found consistently in microbiological series reported in the literature. In series of patients with VAP diagnosed using either a

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**Table 2—Microorganisms Recovered in Significant Amounts From Quantitative Distal Cultures in 29 Episodes of OCC-VAP**

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus spp</td>
<td>12</td>
</tr>
<tr>
<td>Neisseria spp</td>
<td>7</td>
</tr>
<tr>
<td>CGNS</td>
<td>6</td>
</tr>
<tr>
<td>H. parainfluenzae</td>
<td>4</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>4</td>
</tr>
<tr>
<td>Corynebacterium striatum</td>
<td>1</td>
</tr>
</tbody>
</table>

Clinical Investigations in Critical Care
noninvasive\textsuperscript{15–17} or an invasive strategy.\textsuperscript{17–21} OCCs contributed 2.6 to 36% of organisms recovered in significant concentrations. Interestingly, studies comparing histologic and microbiological criteria for VAP diagnosis have yielded conflicting data. In two studies,\textsuperscript{25,29} significant OCC growth was not found in cultures of biopsies from lungs with histologic pneumonia, whereas in two others\textsuperscript{13,14} OCCs contributed 8% and 10%, respectively, of the microorganisms recovered in significant amounts in lung biopsy cultures. OCCs accounted for 0%\textsuperscript{,29} 11%\textsuperscript{,28} and 60%\textsuperscript{,13} of the significant cultures of distal samplings in VAP episodes with histologic findings of pneumonia. Moreover, OCCs are chiefly encountered in polymicrobial VAP. Finally, the meaning of significant growth in quantitative cultures of OCCs only remains unclear.

For respiratory infection to occur, at least one of the three following factors must be present: immunodeficiency in the host; an inoculum of microorganisms into the lower respiratory tract that is large enough to overwhelm the host’s immune system; or a highly virulent organism. One or more of these three factors were present in our exposed patients.

Many ICU patients have prevalent underlying factors associated with immunodeficiency, such as diabetes mellitus or glucocorticoid therapy. These factors increase the risk of infectious and noninfectious life-threatening events. More importantly, there is ample evidence that critical illness is associated with immune defense impairment. Impairments in neutrophil functions including decreased chemotaxis, poor opsonization, and a limited bactericidal effect have been reported in ICU patients.\textsuperscript{30}

Anergy is common in critically ill patients.\textsuperscript{31,32} A large body of data suggests that, during sepsis, the early inflammatory phase that is driven by inflammatory cytokine production is counterbalanced by a subsequent anti-inflammatory phase (the compensatory anti-inflammatory response syndrome), which can lead to immunodeficiency.\textsuperscript{11} Moreover, many studies\textsuperscript{12,33,34} have found impairment of local immune defenses in the lungs; endotracheal intubation provides microorganisms with direct access to the distal airways and impairs coughing and mucociliary function. Furthermore, sepsis is associated with decreased neutrophil recruitment and impaired alveolar macrophage function. Finally, cytokine network dysregulation with interleukin-10 production may lead to local immunosuppression.\textsuperscript{35} Interestingly, in a study of VAP in trauma patients, a population in which abundant evidence of immunosuppression has been reported, 45% of the microorganisms were OCCs. In addition, therapy with glucocorticoids is being used increasingly in ICUs for the treatment of various conditions,\textsuperscript{36} resulting in additional immunosuppression.

Of the OCC-VAP episodes in our study, 76% occurred within 8 days after intubation or extubation, suggesting that the inhalation of oropharyngeal secretions occurring during these procedures or caused during the following days by swallowing dysfunction may increase the risk of OCC-VAP. A study by Valles and coworkers\textsuperscript{37} of continuous subglottic secretion aspiration in intubated patients supports this hypothesis. Continuous aspiration was
associated with significant reductions in the numbers of Gram-positive cocci and Haemophilus spp and in the incidence of VAP during the first 5 days of IMV, as well as with a significantly greater volume of subglottic secretions aspirated daily in the patients without VAP. The pathophysiology of CGNS-VAP is unclear. Although unlikely, we cannot exclude contamination by organisms on the hands of the nurses who performed aspirations. Hematogenous seeding is another possibility.

Oropharyngeal microorganisms such as viridans streptococci,9,10 H parainfluenzae,7 Neisseria spp,5,6 and M catarrhalis38 have been described in patients with community-acquired pneumonia, and M catarrhalis has been described in those with nosocomial pneumonia.39 Viridans streptococci10,13,14 and, less frequently, M catarrhalis38 have been reported to cause lethal pneumonia. In patients with VAP caused by oropharyngeal microorganisms, viridans streptococci have been recovered from blood,10 abscess pus,8 and postmortem lung biopsy specimens13,14; M catarrhalis38 has been recovered from blood; and N mucosa has been recovered from pleural fluid.40 Most of these patients were immunodeficient (although those patients with AIDS or hematologic malignancies were not included), but some had normal immune defenses. These clinical data are supported by \textit{in vitro} findings such as the presence of protease production by viridans streptococci.41

Our study provides six sources of support for the possibility that OCCs may cause VAP. First, for 14 of the 29 patients, the three experts who independently and blindly reviewed the medical records all gave a diagnosis of OCC-VAP, although the distal bronchial samples showed only one or more OCCs. Second, a microbiological diagnosis of OCC-VAP was associated with a significant increase in LOD scores during the 3 days before the bronchoscopy, whereas no significant change was seen in the matched no-VAP patients during the corresponding hospitalization days \((p = 0.18 \ [\text{Wilcoxon test}]).\) Moreover, ICU stay duration was significantly longer in the OCC-VAP group. However, the crude mortality rate was identical among OCC-VAP and no-VAP patients, and, after adjustment for severity scores, no excess mortality was found in the OCC-VAP patients \((\text{OR, 1.19; 95\% CI, 0.41 to 3.46; } p = 0.8).\) The power of the exposed/unexposed study was perhaps too small to detect a small increase in mortality in the OCC-VAP group. Third, the CPIS was > 6 in 20 cases and was 6 in 4 additive cases. Fourth, postmortem histologic findings were consistent with VAP caused by OCCs in two patients, and CT scans of the chest showed lung abscesses in two other episodes. Fifth, the results of both PSB specimen and BAL fluid cultures

<table>
<thead>
<tr>
<th>Variables</th>
<th>OCC-VAP ((n = 28))</th>
<th>No VAP ((n = 56))</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS II score</td>
<td>38.3 ± 16</td>
<td>39.2 ± 15.2</td>
<td>0.26</td>
</tr>
<tr>
<td>Transfer from hospital ward</td>
<td>21 (75)</td>
<td>37 (66)</td>
<td>0.15</td>
</tr>
<tr>
<td>Age, yr</td>
<td>67.6 ± 10</td>
<td>67.8 ± 9</td>
<td>0.93</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
<td>42</td>
<td>0.08</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>14</td>
<td>26</td>
<td>0.48</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>9</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>5</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>LOD score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On hospital admission</td>
<td>6.2 ± 3.8</td>
<td>4.8 ± 2.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Day 3</td>
<td>3.8 ± 2.5</td>
<td>4.4 ± 1.9</td>
<td>0.87</td>
</tr>
<tr>
<td>Day 0</td>
<td>5.93 ± 2.7</td>
<td>4.4 ± 1.9</td>
<td>0.0009</td>
</tr>
<tr>
<td>Main diagnosis on hospital (admission)</td>
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<td></td>
</tr>
<tr>
<td>Multiple organ failure</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>8</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>10</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Duration of ICU stay, d</td>
<td>26.9 ± 22</td>
<td>20.3 ± 19</td>
<td>0.024</td>
</tr>
<tr>
<td>In-ICU deaths</td>
<td>10 (36)</td>
<td>20 (36)</td>
<td>1</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD or No. (%), unless otherwise indicated.
†Characteristics of patients were compared using two-way analysis of variance on ranks for continuous data and a two-covariates logistic model for qualitative data (in both cases, one factor was exposure and the other was the triplet composed of an OCC-VAP patient and two matched No-VAP patients).

Table 4—Subjects Included in the Exposed/Unexposed Study*
were above the cutoffs in 13 episodes. Moreover, the presence of > 5% ICOs in 40% of OCC-VAP patients establishes that these pathogens can mount a significant local inflammatory response. Finally, the outcomes for the seven patients not treated or inefficiently treated are worrying. Three patients died, one with histologic findings that were consistent with VAP and one after the development of a lung abscess.

However, the significant growth of OCCs in distal bronchial samples may reflect the contamination of the samples during collection or the nonpathogenic colonization of the lung. We used standard sampling techniques that are designed to minimize the risk of contamination. In 11 OCC-VAP episodes, there was another condition that could have explained both the fever and the new radiographic infiltrates. However, alternative diagnoses are often present in patients with VAP caused by classic nosocomial pathogens. The percentage of squamous epithelial cells, an indicator of oropharyngeal contamination, was < 1% in all episodes. Another issue is the specificity of positive distal samples for the diagnosis of VAP. In a study of mechanically ventilated patients without signs or symptoms of pulmonary infection and without radiographic infiltrates, the specificities of PSB specimen and BAL fluid cultures were low (59% and 65%, respectively), and the rate of false-positive results was high (41% and 35%, respectively), when 10^3 cfu and 10^4 cfu/mL, respectively, were used as the cutoffs for PSB specimen and BAL fluid cultures. However, the patients received antibiotics before sample collection. In contrast, in a study comparing the PSB procedure and BAL in patients with no recent antibiotic therapy changes, the specificities of the PSB procedure and BAL for the diagnosis of VAP were 89% and 78%, respectively, the standard being histologic and microbiologic lung specimen findings immediately after death. In addition, a recent meta-analysis showed that PSB specimen and BAL fluid cultures are reliable for the diagnosis of VAP, particularly in patients with no recent antimicrobial treatment change. Moreover, in 14 of the episodes, the results of at least two microbiological tests (e.g., BAL fluid smears, BAL fluid cultures, and/or PSB specimen cultures) were positive. This lends strength to our findings, as specificity has been shown to be better when the results of two or all three tests are positive.

Finally, the degree of confidence with the definite diagnosis between experts was good in only 56% of cases. This was due mainly to the high number of patients with possible or probable alternate diagnoses. Moreover, the confidence in the quantitative bacteriologic results has been probably decreased by the known low pathogenicity of encountered microorganisms.

Finally, the main issue is the relevance of our findings to the treatment of patients with suspected OCC-VAP. Unnecessary antibiotic therapy in a patient with lung colonization can induce the emergence of drug-resistant strains, but a failure to treat VAP increases the risk of morbidity and mortality. Oropharyngeal organisms are susceptible to co-amoxiclav or third-generation cephalosporins and, consequently, the American Thoracic Society guidelines for VAP management are valid. CGNS was the only microorganism in five patients with VAP occurring more than 5 days after intubation. In patients with late-onset VAP, the finding of Gram-positive cocci on BAL fluid smears should lead to the administration of vancomycin because it can reflect pneumonia caused by a methicillin-resistant Staphylococcus aureus. Consequently, when identification studies show that the Gram-positive organism is a CGNS, the problem is not whether vancomycin should be added to the antibiotic regimen but whether vancomycin should be continued. Because most CGNS strains are resistant to co-amoxiclav, cephalosporins, and methicillin, the recovery of a CGNS sometimes leads to vancomycin prescription. However, few data are available on the pathogenicity of CGNS in the lungs, which remains a matter of debate. Very few well-documented case reports of CGNS pneumonia have been reported: one case of Staphylococcus saprophyticus pneumonia in an ICU patient; one case of Staphylococcus cohnii community-acquired pneumonia in an AIDS patient; and one case of Staphylococcus epidermidis VAP with histologic findings of pneumonia. In our study, there was no alternative diagnosis in one of our CGNS cases, and the two patients with lung abscesses had Staphylococcus epidermidis as the only distal bronchial microorganism. Consequently, in a critically ill patient whose status is deteriorating and who has significant amounts of CGNS in distal bronchial quantitative cultures with no firm evidence of another cause, we believe that antibiotics against CGNS should be given.

In conclusion, OCC-VAP accounted for 9% of VAP episodes in our study and was associated with worsening organ dysfunction scores. Although alternative conditions explaining chest abnormalities and fever are common, a new radiographic infiltrate with significant growth in distal bronchial cultures of commensal microorganisms only is highly suggestive of VAP. We suggest that such a condition should be systematically treated except in the case of a stable patient with a strong alternative diagnosis for the lung infiltrate and fever for which the treatment should be discussed case by case. OCCs may have
the same deleterious effects as classic nosocomial pathogens in critically ill patients.

REFERENCES
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