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*Chest* 2008;134;101-108; Prepublished online April 10, 2008;
DOI 10.1378/chest.07-2546

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(http://chestjournal.chestpubs.org/site/misc/reprints.xhtml)
ISSN:0012-3692
Prognostic Role of Clinical and Laboratory Criteria To Identify Early Ventilator-Associated Pneumonia in Brain Injury*

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Background: We investigated the role of the clinical pulmonary infection score (CPIS), serum levels of procalcitonin (PCT), C-reactive protein (CRP), and serum amyloid A (SAA) in the detection of patients with early ventilator-associated pneumonia (VAP).

Methods: Observational study in a university hospital. In 58 patients with severe brain injury receiving mechanical ventilation, CPIS, PCT, CRP and SAA were evaluated at ICU entry and at days 3 to 4 of hospital stay for VAP diagnosis (confirmed by endotracheal aspirate or BAL cultures).

Results: We found the following: (1) PCT at entry was increased in patients who later had early VAP develop (25 patients) compared to no VAP (median, 1.4 ng/mL; 25–75 percentiles, 0.14–0.78; vs median, 0.2 ng/mL; 25–75 percentiles, 0.76–2.4, p < 0.001; sensitivity, 76%; and specificity, 75%); (2) CPIS increased at the day of VAP diagnosis, compared to entry (median, 6.6 ± 1.1 vs 1.5 ± 1.1, p < 0.001; sensitivity, 97%; specificity, 100%), while other serum inflammatory markers did not change; and (3) deterioration in oxygenation and changes in tracheal secretions were the main determinants of CPIS changes.

Conclusions: PCT may be a useful marker to predict which patients subsequently have early VAP. The CPIS could help as an early way to detect the patients with early VAP and who need further diagnostic testing.

Key words: brain injury; clinical infection pulmonary score; C-reactive protein; procalcitonin; serum amyloid A; ventilator-associated pneumonia

Abbreviations: CPIS = clinical pulmonary infection score; CRP = C-reactive protein; Fio₂ = fraction of inspired oxygen; GCS = Glasgow coma scale; PCT = procalcitonin; SAA = serum amyloid A; VAP = ventilator-associated pneumonia

Patients with severe brain injury are at increased risk for ventilator-associated pneumonia (VAP), with a worsening of neurologic outcome, and increased ICU and hospital stay, mortality, and costs. Delays in the correct diagnosis and antibiotic administration have been found to increase hospital mortality; thus, rapid identification of VAP is required in an attempt to improve outcome.

The number of invasive diagnostic procedures should be minimized in severe brain-injured patients. The results of the quantitative cultures are not generally promptly available, and clinical signs of infection are poorly sensitive and specific. The diagnostic yield of these variables may increase when they are combined in the clinical infection pulmonary score (CPIS). Moreover, acute-phase inflammatory markers have been found to be poorly associated with the onset of VAP, while procalcitonin (PCT) has been reported to be a helpful parameter in the early diagnosis of VAP and serum amyloid A (SAA) an appropriate marker of infections. In brain-injured patients, the serial measurement of PCT as a possible marker of the inflammatory process or as a diagnostic tool for VAP has not been reported.

In this study, we investigated a selected population of severe traumatic and nontraumatic brain-injured
patients to evaluate the following: (1) the serial changes in acute-phase inflammatory markers (PCT, SAA, and CRP) in the early phase after trauma and their relation to clinical evolution; (2) and the role of clinical criteria, the CPIS, serum PCT, and SAA concentrations in the detection of patients with early VAP.

**Materials and Methods**

**Patient Selection**

Sixty-seven brain-injured patients admitted to the ICU of the Servizio Anestesia B, Ospedale di Circolo e Fondazione Macchi, Insubria University, Varese, Italy were identified over a 1-year period. The study was approved by the Ethical Committee of the Hospital and performed in accordance with the precepts established by Helsinki Declaration. Inclusion criteria were as follows: (1) severe brain injury, defined as a Glasgow coma scale (GCS) score at hospital entry ≤ 8, due to isolated brain trauma or spontaneous parenchymal hemorrhage; and (2) intubation and mechanical ventilation. Exclusion criteria were as follows: (1) age < 18 years; (2) severe disease without any possibility of favorable outcome: brain death or cardiac arrest before ICU entry; (3) positive culture findings of tracheal aspirate or the BAL with evidence of pneumonia at the time of ICU admission; and (4) presence of any organ failure other than the brain. We excluded patients with respiratory failure due to pulmonary injury but allowed the use of ventilatory support for airway protection in the setting of severe neurologic injury.

Clinical treatment was performed according to general recommendations. All patients received antibiotic prophylaxis with ampicillin/sulbactam for the first 3 days of ICU entry.

**Clinical and Laboratory Variables**

**Clinical Evaluation and CPIS:** As shown in Table 1 CPIS calculation was made by modified original score as described by Pugin et al.7 We also computed a simplified CPIS not including the chest radiographic score (simplified CPIS).

**Acute-Phase Inflammatory Markers:** PCT serum concentrations were determined using an immunoluminometric assay (LUMI test PCT; Brahms Diagnostic; Berlin, Germany). For this assay, the lower limit of detection is approximately 0.16 ng/mL, and the standard curve ranges between 0.08 ng/mL and 500 ng/mL. The upper reference limit reported in the package insert for PCT was 0.5 µg/L.

SAA serum concentrations were determined using a latex-enhanced nephelometric immunoassay (N Latex SAA; Dade Behring; Marburg, Germany). For this assay, the lower limit of detection is 2.6 mg/L, and the standard curve ranges between 3 mg/L and 200 mg/L. The upper reference limit reported in the package insert for SAA was 10.2 mg/L.

CRP serum concentrations were determined using a immunoturbidimetric assay (CRP Latex; Olympus Diagnostica; Hamburg, Germany). For this assay, the lower limit of detection is 1.38 mg/L, and the standard curve ranges between 5 mg/L and 170 mg/L. The upper reference limit reported in the package insert for CRP was 5 mg/L.

**VAP Definition**

The diagnosis of VAP required not only positive results of tracheal aspirate quantitative cultures (≥10⁶ cfu/mL) but also a positive chest radiograph and clinical features be present according to American Thoracic Society guidelines.14 The tracheal aspirate or BAL were performed as generally recommended.14-18 Severity of the bacterial infection was based on the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference criteria.17 VAP patients with severe sepsis or septic shock were classified as severe VAP.

**Protocol for Sampling**

Clinical evaluation, CPIS, acute-phase inflammatory markers (PCT, CRP, SAA), and cultures including endotracheal aspirate or BAL, were performed in all the patients at ICU entry (at entry). Based on our standard pattern of practice, we estimate that the actual delay in time between injury (or arrival in emergency department) and initial sampling ranged between 5 to 6 hours.
Table 2—Demographics, Clinical Data, and Outcome Data*

<table>
<thead>
<tr>
<th>Variables</th>
<th>No Early VAP</th>
<th>Early VAP Overall</th>
<th>No Severe Early VAP</th>
<th>Severe Early VAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>33</td>
<td>25</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>18/15</td>
<td>17/8</td>
<td>7/5</td>
<td>10/3</td>
</tr>
<tr>
<td>Age, yr</td>
<td>48.5 ± 16.8</td>
<td>50.6 ± 15.7</td>
<td>54.8 ± 20.0</td>
<td>46.8 ± 9.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.4 ± 2.8</td>
<td>25.1 ± 2.6</td>
<td>25.6 ± 3.1</td>
<td>24.6 ± 2.0</td>
</tr>
<tr>
<td>Simplified acute physiology II score</td>
<td>37.0 ± 10.1†</td>
<td>42.0 ± 8.2</td>
<td>39.8 ± 8.6</td>
<td>44.0 ± 7.6</td>
</tr>
<tr>
<td>Brain trauma/no trauma, No.</td>
<td>14/19</td>
<td>14/11</td>
<td>5/7</td>
<td>9/4</td>
</tr>
<tr>
<td>GCS score at ICU entry</td>
<td>5.5 ± 1.5</td>
<td>5.3 ± 1.3</td>
<td>5.3 ± 1.4</td>
<td>5.3 ± 1.3</td>
</tr>
<tr>
<td>GCS score at ICU discharge</td>
<td>14.5 ± 1.4†</td>
<td>10.0 ± 2.9</td>
<td>9.5 ± 2.8</td>
<td>10.6 ± 3.1</td>
</tr>
<tr>
<td>ICU stay, d Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>6.2 ± 4.1†</td>
<td>25.5 ± 17.3</td>
<td>30.5 ± 20.9</td>
<td>20.5 ± 11.9</td>
</tr>
<tr>
<td>Survivors</td>
<td>8.0 ± 3.2†</td>
<td>29.1 ± 17.3</td>
<td>33.4 ± 20.1</td>
<td>23.8 ± 12.3</td>
</tr>
<tr>
<td>Twenty-eight-day mortality, %</td>
<td>24</td>
<td>28</td>
<td>25</td>
<td>30</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.
†p = 0.048 vs early VAP overall.
‡p < 0.001 vs early VAP overall, no severe early VAP, and severe early VAP.

Figure 1. Top left panel: PCT (median, tenth, twenty-fifth, seventy-fifth, and ninetieth percentiles as vertical boxes with error bars and outlier data) at entry, study day, and study day +1 in no early VAP, early VAP overall, nonsevere early VAP, and severe early VAP. #p < 0.001 vs early VAP overall (at entry); *p < 0.001 vs severe early VAP (at entry); †p = 0.021 vs severe early VAP (study day); ‡p = 0.026 vs severe early VAP (study day +1). Top right panel: SAA (median, tenth, twenty-fifth, seventy-fifth, and ninetieth percentiles as vertical boxes with error bars and outlier data) at entry, study day, and study day +1, in no early VAP, early VAP overall, nonsevere early VAP, and severe early VAP. #p < 0.001 vs early VAP overall (at entry); *p = 0.007 vs no early VAP (study day). Bottom left panel: CRP (median, tenth, twenty-fifth, seventy-fifth, and ninetieth percentiles as vertical boxes with error bars and outliers data) at entry, study day, and study day +1, in no early VAP, early VAP overall, nonsevere early VAP, and severe early VAP. #p = 0.004 vs early VAP overall (at entry); ‡p = 0.034 vs no early VAP (study day).
15 h, without any differences between the groups. Measurements and cultures were repeated after 3 to 4 days from entry (study day) and 1 day after the study day (study day + 1), if the temperature was ≥ 38°C.

Thus, we were able to classify the patients in two groups: (1) patients without pneumonia at entry and at the study day (no early VAP group); and (2) patients without pneumonia at entry but who had VAP at the study day (early VAP group). We further divided the VAP group into patients with VAP associated with signs of severe sepsis or septic shock (severe early VAP group), and patients with VAP not associated with severe sepsis or septic shock (no severe early VAP group). Study days were 3.4 ± 0.5 days and 3.5 ± 0.6 days after entry in the early VAP group and no early VAP group, respectively.

Statistical Methods

Data are shown as mean ± SD unless otherwise indicated. From previous studies, we computed that at least 15 patients with and without VAP were necessary to show a difference in PCT levels and CPIS with a power of 80% and an α error (at two tails) of 0.05. The SigmaStat statistical and SigmaPlot plotting packages (Systat Software; Chicago, IL) were used to analyze and plot the experimental data. Statistical analysis was performed by Student t test and Mann-Whitney rank-sum test (when the normality test was violated); p < 0.05 was considered as significant.

RESULTS

Clinical Characteristics and Acute-Phase Inflammatory Markers at Entry

We screened a total of 101 patients. We excluded 2 patients due to age < 18 years, 3 patients due to extrahospital cardiac arrest or brain death, and 29 patients due to severe multiple trauma.

We included 67 patients with severe brain injury, but 9 patients were further excluded from the analysis due to positive culture finding of the endotracheal aspirate or BAL at entry. The remaining 58 brain-injured patients fulfilling the inclusion criteria were admitted into the study. The diagnosis of early VAP was established in 25 patients: 13 patients had Gram-negative bacilli, 6 patients had Gram-positive cocci, and polymicrobial growth was seen in 6 patients. Patients had no concomitant other infections. Table 2 shows demographic, clinical data, and outcome variables of the overall population. Patients who did have early VAP had an increased ICU stay, with worse GCS score at discharge. Acute-phase inflammatory markers are shown in Figure 1. PCT was increased on entry in early VAP vs no early VAP, and was higher on entry in severe vs nonsevere early VAP. SAA and CRP were higher at entry in early VAP vs no early VAP groups. None of the markers increased significantly from entry with the onset of VAP. In particular, the sensitivity and specificity of PCT and SAA at entry to predict patients with early VAP, independently from its severity, was 76% and 75.8%, respectively (cut-off, 0.77 ng/mL; area under the curve, 0.78) for PCT (Fig 2, top panel) and 84% and 72.7%, respectively (cut-off, 224 mg/mL; area under the curve, 0.76) for SAA. More importantly, PCT but not CRP and SAA was significantly increased at entry and at study day in patients with severe VAP compared to nonsevere early VAP. The sensitivity and specificity of PCT at entry to predict patients with severe early VAP were 92.3% and 90.9%, respectively (cut-off, 1.2 ng/mL; area under the curve, 0.94) [Fig 2, bottom panel].

At entry, none of the variables other than oxygenation were different between those who did not have early VAP and the overall group that had early VAP.
and a specificity 100%.

with a sensitivity of 97.1% and 85.3% respectively

and the CPIS for early detection of patients with

Study day

secretions increased, while PaO₂

increased in the overall early VAP group at study day

Data are presented as mean ± SD.

‡p < 0.001 vs early VAP overall, no severe early VAP, severe early VAP.

†p < 0.001 vs study day.

§p < 0.001 vs study day + 1.

(3.1) In Figure 3, at entry the CPIS and the simplified CPIS were comparable in all groups.

Clinical Characteristics and Acute-Phase Inflammatory Markers for Early VAP Diagnosis

In early VAP group serial measurements of PCT, CRP and SAA were not significantly different at the study day and at study day + 1 compared to entry (Fig 1). At study day, positive end-expiratory pressured was higher (7.7 ± 2.2 cm H₂O vs 4.7 ± 1.1 cm H₂O, p < 0.001) and compliance was lower (62.0 ± 11.3 mL/cm H₂O vs 71.2 ± 7.6 mL/cm H₂O, p < 0.001) in overall early VAP as compared to no early VAP group.

In the overall early VAP group, among clinical criteria (excluding radiographic score), only tracheal secretions increased, while PaO₂/fraction of inspired oxygen (FiO₂) deteriorated at study day and at study day + 1 compared to entry (Table 3), PaO₂/FiO₂ was lower in severe compared to non-severe early VAP at study day and study day + 1.

The total CPIS and the simplified CPIS markedly increased in the overall early VAP group at study day and study day + 1 compared to entry (Fig 3). These data suggest that early VAP can be diagnosed in patients with a CPIS > 3 or a simplified CPIS > 3 with a sensitivity of 97.1% and 85.3% respectively and a specificity 100%.

Discussion

This is the first study investigating the role of PCT and the CPIS for early detection of patients with early VAP in the setting of brain injury. In severe brain-injured patients, the most frequent medical complication is respiratory dysfunction, with an increased mortality and worse neurologic outcome. In this study we investigated changes in CRP, SAA, PCT, and leukocytes. Serum concentrations of PCT have been reported to be markedly increased in a variety of clinical and experimental conditions that lead to systemic inflammation. In many of these studies, the concentrations of PCT reflected the severity of the systemic inflammation and were predictive of mortality.

We observed that in brain-injured patients, an elevated PCT on ICU entry correlated with the subsequent development of early VAP. Patients with VAP had a higher initial PCT than those who did not, although most of the high initial PCT values occurred in patients who had severe VAP, but not in those with nonsevere VAP (Fig 1, top left panel). In addition, those who had VAP had no serial rise in PCT. These findings may mean that either patients with severe VAP had intense inflammation initially, as reflected by high PCT, which predisposed to subsequent pneumonia, or that they had aspirated prior to arrival in the hospital and may already have had a pneumonia, although it was not able to be detected clinically by radiography or by other clinical criteria.

A previous study in brain-injured patients reported that serum PCT appeared to be correlated with the severity of traumatic brain injury and mortality. However, we did not find any significant correlation between the level of PCT and the sever-
Figure 3. Top panel: Total CPIS (mean ± SD) at entry, study day, and study day + 1, in no early VAP, early VAP overall, nonsevere early VAP, and severe early VAP. *p < 0.001 vs early VAP overall (study day), nonsevere early VAP (study day), severe early VAP (study day); #p < 0.001 vs study day and study day + 1. Bottom panel: Simplified CPIS (mean ± SD) at entry, study day, and study day + 1, in no early VAP, early VAP overall, nonsevere early VAP, and severe early VAP. *p < 0.001 vs early VAP overall (study day), nonsevere early VAP (study day), severe early VAP (study day). #p < 0.001 vs study day and study day + 1.

We found that a simplified CPIS > 3 was useful to predict the patients with early VAP as confirmed by invasive techniques. The threshold of the CPIS for VAP diagnosis was lower than that reported previously (> 6) because we selected a group of patients without any previous pulmonary alteration or infection before VAP. Thus, the use of the CPIS could be a useful tool to reduce the number of invasive diagnostic procedures, potentially harmful in brain-injured patients, restricting the use of these techniques to those with an elevated CPIS.

Our study suffers some potential limitations: (1) patients with positive microbiological culture findings at entry were excluded; thus, our results would be less consistent in patients with lung parenchyma infection at entry; (2) some of the patients with negative culture findings could have had infection on entry, overestimating the role of PCT to predict occurrence of early VAP; (3) antibiotic prophylaxis may have impacted the value of PCT measurements and the frequency of pneumonia; (4) CPIS and serum markers were measured by protocol at days 3 to 4 in all patients, and thus it is possible that VAP occurred 1 or 2 days earlier; thus, a persistently elevated PCT level may reflect inappropriate therapy, as previously suggested by Luyt et al; (5) it is possible that PCT values were increased because of trauma itself; and (6) the small sample size studied.

Our results can have potential clinical implications. First, patients with increased PCT were at increased risk for subsequent severe early VAP. Second, we did not find any usefulness to specific acute-phase inflammatory markers at days 3 to 4 to detect patients when they had pneumonia. The use of the CPIS can be useful to define pneumonia patients, mainly from the oxygenation deterioration and the evaluation of tracheal secretions. We suggest that this score be monitored in order to rapidly detect patients with early VAP and to reduce diagnostic procedures in severe brain-injured patients.

The increase in PCT (Fig 1) in those patients destined to get severe early VAP.

Controversy, however, about the clinical diagnosis of VAP continues. The use of the CPIS to detect VAP has been found to be 100% specific and 93% sensitivity in a general population of critically ill patients, but not confirmed in studies. One study in trauma patients, performed on a single-day examination of bacteriologic and clinical parameters, suggested that the CPIS cannot differentiate VAP. Among the different parameters included in the CPIS, we found that the variations in secretions and oxygenation were the most important features. We found that a simplified CPIS > 3 was useful to predict the patients with early VAP as confirmed by invasive techniques. The threshold of the CPIS for VAP diagnosis was lower than that reported previously (> 6) because we selected a group of patients without any previous pulmonary alteration or infection before VAP. Thus, the use of the CPIS could be a useful tool to reduce the number of invasive diagnostic procedures, potentially harmful in brain-injured patients, restricting the use of these techniques to those with an elevated CPIS.

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limiting them only to patients with high CPIS values at the time they demonstrate signs of infection.

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