STABILITY IN COMMUNITY-ACQUIRED PNEUMONIA. ONE STEP FORWARD WITH MARKERS?

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Abstract

Background. Biological markers as expression of systemic inflammation have been recognized as useful to evaluate host response in community-acquired pneumonia (CAP). The objective of our study was to evaluate whether biological markers, namely procalcitonin (PCT) and C reactive protein (CRP) might reflect stability after 72 hours of treatment and absence of subsequent severe complications.

Methods. A prospective cohort study was designed in 394 hospitalized patients with CAP. Clinical stability was evaluated using modified Halm’s criteria: temperature ≤ 37.2ºC; heart rate ≤100 beats/min; respiratory rate ≤24 breaths/min; systolic blood pressure ≥90 mm Hg; and oxygen saturation ≥90% or arterial oxygen partial pressure ≥60 mmHg. PCT and CRP were measured on day 1 and after 72 hours. Severe complications were defined as mechanical ventilation, shock and/or intensive care unit (ICU) admission, or death after 72 hours of treatment.

Results. 220 patients reached clinical stability at 72 hours and had significantly lower levels of CRP (4.2 vs 7 mg/dL) and of PCT (0.33 vs 0.48 ng/mL). Regression logistic analyses were performed to calculate several areas under the ROC curve (AUC) to predict severe complications. The AUC for clinical stability was 0.77; 0.84 (p=0.059) when CRP was added; and 0.77(p=0.45) when PCT was added. When clinical stability was achieved within 72 hours and marker levels were below the cut-off points (0.25 for PCT and 3 for CRP) no severe complications appeared.

Conclusions. Low levels of CRP and PCT at 72 hours in addition to clinical criteria might improve prediction of absence of severe complications.

Words: 250
Introduction.
Prognostic scales provide key information on mortality prediction, but this information is insufficient in the assessment of the response to antibiotic treatment and of clinical stability. [1] The concept of clinical stability is very important for the clinician since it allows decision-making concerning hospital discharge and treatment length. The publication of stability clinical criteria by Halm et al [2] provided a fundamental basis to define this concept which has already been included in guidelines. [3] Nevertheless, occasionally clinical criteria are difficult to evaluate in elderly patients with low clinical expression, with multiple associated diseases or with chronic respiratory insufficiency. Because of this, it would be of great interest to have objective and easily measurable data indicating existence of “biological stability”.

Markers such as CRP and PCT have been used to quantify severity, systemic inflammation and prognosis. [4-9] It has been observed that elevation of markers and cytokines within 72-hours from hospitalisation is associated with treatment failure and poor evolution. [1] Furthermore, the reduction of these levels is associated with a good response. [1,8,9] An interesting perspective would be to evaluate the usefulness of markers in providing information on the resolution of the degree of inflammation after the antibiotic treatment. It is known that 72 hours after an adequate treatment, concentration of microorganisms is drastically reduced[10] and, in fact, clinical stability is then reached. [2,11] Our hypothesis is that when clinical stability is reached, reduction of markers is larger, due to the fact that systemic inflammation has low and safe levels for the patient. If this is demonstrated, levels of systemic markers could be used either on their own or jointly with clinical criteria of stability in order to decide safely if there is subsequent risk for the patient.

Objectives are firstly, to investigate if there exists a correlation between clinical stability and levels of biological markers; secondly, to evaluate whether biomarkers and/or assessment of clinical stability criteria can predict absence of severe complications; and thirdly, to find or define the best cut-off points of PCT and CRP permitting to identify the absence of severe complications or poor prognosis after 72 hours of antibiotic treatment.

PATIENTS AND METHODS
A prospective longitudinal study was conducted in patients with CAP consecutively hospitalized in two tertiary-care teaching hospitals from October 2003 to June 2004. Inclusion criteria were a new radiographic infiltrate compatible with the presence of acute pneumonia and at least two signs or symptoms of CAP (e. g. temperature >38ºC, productive cough, chest pain, shortness of breath, crackles on auscultation). Exclusion criteria were admission within the previous 15 days, nursing-home patients, immunosuppressive treatment and/or steroids (>15 mg/day), leukocyte count <1,000/mm3 or neutrophil count <500/mm3 (except if attributable to CAP). The study was approved by two Ethics Committees and the patients signed an informed consent.

Data collection:
Data on age, gender, smoking and alcohol habits (>80 g/day), prior influenza vaccination with that year’s trivalent inactivated influenza vaccine before developing pneumonia, co-morbid diseases such as chronic obstructive pulmonary disease (COPD), and cardiac, liver, renal or central nervous system (CNS) disorders were collected. Recorded clinical signs and symptoms were: cough, expectoration, pleuritic chest pain, dyspnea, acute confusion, temperature, respiratory and heart rates, systolic and diastolic blood pressure and the presence of rales. The following analytical data were recorded: leukocyte count, Na, K, serum creatinine, ALT/AST and arterial blood gas analysis. On admission, Fine risk classes [12] and CURB-65 were also recorded. [13] Initial empirical antimicrobial treatment was recorded and classified as follows: beta-lactam (ceftriaxone/cefotaxime or co-amoxi-clavulanate) with a macrolide (clarithromycin or azithromycin), fluoroquinolone (levofloxacin), beta-lactam with quinolone, beta-lactam as monotherapy, and other regimens. Surviving patients underwent radiological and serologic follow-up after 30 days.

Definitions.
Clinical stability was defined following a slight modification of Halm’s criteria [2,11] as the condition when the following threshold values were achieved for all parameters: temperature ≤37.2 ºC, heart rate ≤100 beats/min, respiratory rate ≤24 breaths/min, systolic
blood pressure ≥ 90 mm Hg, and oxygen saturation ≥90% or Pa O₂ ≥60 mm Hg when the patient was not receiving supplemental oxygen. In patients with home oxygen therapy stability was considered when their oxygen needs were the same as prior to admission.

The primary outcome—severe complications after 72 hours of treatment—was defined as death after 72 hours of treatment and within 30 days of admission; apparition of shock or need of mechanical ventilation (invasive or non-invasive); or intensive care unit (ICU) admission after 72 hours of treatment.

**Determination of cytokines, PCT and CRP.**

Blood samples were drawn on the first day. Blood was centrifuged, coded and frozen at ~80 °C until subsequent analyses. Determination of IL-6, IL-8, IL-10 and TNF-α was performed with a commercial enzyymoimmunoassay technique (Biosource, Nivelles, Belgium). Limits of detection were 3 pg/mL for TNF-α; 2 pg/mL for IL-6; 0.7 pg/mL for IL-8; and 1 pg/mL for IL-10.

An immunoluminometric technique was used to measure PCT (Liaison Bhams PCT, DiaSorin, Saluggia, Italy) with a detection limit of 0.3 ng/mL. CRP was measured using an immunoturbidimetric method using a commercially available test (Bayer Diagnostics) with an Advia 2400, with a detection limit of 1.5 mg/dL.

**Statistical analysis**

Statistical analysis was performed using software (SPSS 15.0). The chi-square test was used for qualitative variables, and the Student’s t or Mann-Whitney U tests for quantitative variables. Correlation was analysed using the Spearman’s rho correlation analysis.

Several multivariate logistic regression analyses were performed to predict absence of severe complications after day 3 (dependent variable). Independent variables were clinical stability within the first 72 hours of treatment, levels of CRP on day 3 and levels of PCT on day 3.

In order to calculate the predictive value of markers (CRP and PCT) together with clinical criteria of stability, the area under the ROC curve was calculated from the multivariate logistic regression analyses performed with several combinations. For each regression logistic model, the area under the ROC curve (AUC) was calculated for absence of severe complications. Statistical comparison of AUCs was conducted according to the Hanley and McNeil method;[14] p values <0.05 were considered significant. For resulting models, sensitivity, specificity and positive and negative predictive values were calculated. Hosmer and Lemeshow goodness-of-fit test was performed for each model.[15]

**RESULTS**

**Patient population**

During the study period 394 patients with a mean age of 66.5±17.2 years were included. Clinical stability after 72 hours of antibiotics was reached by 220 patients (55.8%). Main demographic characteristics, comorbidity and initial severity in the two groups with clinical stability at 72 hours or later are shown in Table 1. Prescribed initial antimicrobial treatments were: 250 (58.3%) beta-lactam (ceftiraxone/cefotaxime or co-amoxiclavulanate) plus macrolide (clarithromycin or azithromycin), 99 (23.1%) fluoroquinolone (levofloxacin), 29 (6.8%) beta-lactam plus quinolone, 24 (5.6%) beta lactam as monotherapy, and 27 (6.3%) other regimens. The differences between groups are shown in table 1.

**Table 1. Characteristics, comorbidity and initial severity, and clinical stability.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Stability</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤3 days n=220 (55.8%)</td>
<td>&gt;3 days n=174 (44.2%)</td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>65 ± 17</td>
<td>67 ± 18</td>
</tr>
<tr>
<td>Gender -F/M (%)</td>
<td>76/144(34.5/65.5)</td>
<td>72/102(41.4/58.6)</td>
</tr>
</tbody>
</table>
24 patients (5.6%) died during hospitalization. Mortality within 30 days was 6.8% (29 patients). After 72 hours of treatment, 31 patients (7.2%) developed severe complications: 4 were admitted to ICU, 8 required mechanical ventilation, 10 suffered from shock and 23 died.

Most frequently found microorganisms were: 79 S. pneumoniae (20%), 17 Legionella pneumophila (4.3%), 10 S. aureus (2.5%), 11 H. influenza (2.8%), 10 Pseudomonas aeruginosa (2.5%), 5 Escherichia coli (1.3%), 5 Mycoplasma pneumonia (1.3%) and 27 other microorganisms. We found mixed aetiology in 24 patients: 14 of them had S. pneumoniae together with other microorganisms.

Clinical stability and markers.

Univariate analyses

Results of markers CRP and PCT according or not to the clinical stability are shown in Table 2.

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>≤3days Median (P_{25}–P_{75})</th>
<th>&gt;3days Median (P_{25}–P_{75})</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/dl</td>
<td>12.2 (5.9–21.6)</td>
<td>17.3 (10.4–28.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>PCT, ng/ml</td>
<td>0.43 (0.24–1.72)</td>
<td>0.93 (0.34–4.31)</td>
<td>0.0003</td>
</tr>
<tr>
<td>TNF-1, pg/ml</td>
<td>27 (16–45)</td>
<td>31 (19–48)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

F/M, female/male; COPD, chronic obstructive pulmonary disease; PSI, pneumonia severity index (Fine risk class) #: other antibiotic regimens.
IL-1, pg/ml | 21 (7-36) | 18 (0-30) | 0.08  
IL-6, pg/ml | 63 (25-150) | 101 (47-267) | 0.0003  
IL-10, pg/ml | 5(0-17) | 10 (3-19) | 0.004  
IL-8, pg/ml | 6(2-14) | 6 (2-15) | 0.9

DAY 3
CRP, mg/dl | 4.2 (1.8-9.8) | 7.0 (2.8-14.2) | 0.0003  
PCT, ng/ml | 0.33 (0.17-0.60) | 0.48 (0.25-1.09) | 0.003  
TNF-1, pg/ml | 26 (14-43) | 28 (14-47) | 0.4  
IL-1, pg/ml | 13 (4-28) | 14 (3-25) | 0.8  
IL-6, pg/ml | 24 (7-75) | 49 (16-111) | 0.003  
IL-10, pg/ml | 4(0-14) | 6 (2-19) | 0.03  
IL-8, pg/ml | 7(2-14) | 6 (2-15) | 0.9

CRP, C-reactive protein mg/dl; PCT, procalcitonin ng/ml; TNF-1, IL-1, IL-6, IL-8 and IL-10 pg/ml

Medians of CRP, PCT, IL-6 and IL-10 were significantly higher in patients who did not reach clinical stability at day 3 (Figure 1). Cut-off points of markers to predict absence of severe complications were selected with the highest specificity and positive predictive value, in order not to underestimate any severe complication. After day 3, 5 patients out of 103 with PCT <0.25 ng/ml developed severe complications, whereas 22 out of 213 patients with higher levels did, p<0.05. Regarding day 3 CRP <3 mg/dl; 3 out of 105 patients developed severe complications versus 24 out of 214 patients with higher levels, p<0.05. 15 patients reached CRP < 3 mg/dl and PCT <0.25 ng/ml but did not reach clinical stability by clinical criteria, and 2 patients had subsequent severe complications (13.3%): 1 death and one severe respiratory insufficiency with non-invasive mechanical ventilation.

135 patients reached clinical stability on day 3, but PCT and CRP levels remained high, complications aroused in 3 patients (2.2%), 1 presented septic shock and 2 were deceased.

When clinical stability is also included in the prediction, results are the following: clinical stability reached and PCT below 0.25 no patient (0/28) developed severe complications versus 28/291 who did, p<0.015. Similar findings were reported for CRP ≤3 and clinical stability on day 3: 0/30 developed severe complications versus 30 out of 293 patients without stability and higher CRP levels, p<0.012. The diagnostic value to identify the absence of severe complications is depicted in Table 3.

Table 3. Predictive value of stability clinical criteria and biomarkers (on day 3) for the absence of severe complications after 72 hours.

<table>
<thead>
<tr>
<th>Clinical criteria and Biomarkers</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>OR(95% CI)</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Stability</td>
<td>58%</td>
<td>83%</td>
<td>99%</td>
<td>9%</td>
<td>6.8(2.0-22.4)</td>
<td>3.5(1.5-9.9)</td>
<td>0.5(0.4-0.7)</td>
</tr>
<tr>
<td>CRP&lt;3</td>
<td>35%</td>
<td>89%</td>
<td>97%</td>
<td>11%</td>
<td>4.2(1.3-13.7)</td>
<td>3.1(1.2-9.1)</td>
<td>0.7(0.6-0.9)</td>
</tr>
<tr>
<td>PCT&lt;0.25</td>
<td>34%</td>
<td>81%</td>
<td>95%</td>
<td>10%</td>
<td>2.2(0.8-5.9)</td>
<td>1.8(0.9-4.2)</td>
<td>0.8(0.7-1.05)</td>
</tr>
<tr>
<td>Clinical Stability +CRP&lt;3</td>
<td>19%</td>
<td>100%</td>
<td>100%</td>
<td>10%</td>
<td>14.1(1.4-138.8)</td>
<td>11.4(1.3-110.0)</td>
<td>0.8(0.7-0.9)</td>
</tr>
<tr>
<td>Clinical Stability +PCT&lt;0.25</td>
<td>19%</td>
<td>100%</td>
<td>100%</td>
<td>10%</td>
<td>13.4(1.4-131.7)</td>
<td>10.8(1.3-104.0)</td>
<td>0.8(0.7-0.9)</td>
</tr>
<tr>
<td>Clinical Stability +CRP&lt;3 and PCT&lt;0.25</td>
<td>9%</td>
<td>100%</td>
<td>100%</td>
<td>9%</td>
<td>5.8(0.6-57.5)</td>
<td>5.3(0.6-51.4)</td>
<td>0.9(0.8-1.1)</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value; OR(95% CI), odds ratio (95% confidence interval); LR+, positive likelihood ratio; LR-, negative likelihood ratio
When both markers are added to clinical stability criteria, predictive value does not increase.

**Multivariate analyses**

Three logistic regression analyses were performed to predict severe complications after 72 hours of treatment (dependent variable). The first model included clinical stability and levels of CRP day 3 as independent variable, the second model included clinical stability and levels of PCT, and the third model, clinical stability and levels of CRP and PCT. Clinical stability was a significant independent predictor for the absence of severe complications 0.78 (0.71-0.86). CRP was also found an independent significant predictor 0.86 (0.77-0.97) whereas PCT was not independently associated 1.17 (0.78-1.76).

The AUCs of the different logistic regression models with combinations of markers and clinical stability were calculated. The AUC to predict absence of severe complications after day 3 using clinical stability was 0.77 (95% CI 0.64-0.90); when the CRP value was added, the area increased to 0.84 (0.75-0.92), p=0.059; and when PCT was added, it reached 0.77 (0.63-0.91), p=0.45.
Discussion

The most important findings of our study are firstly, that markers improve safety in the prediction for absence of complications with respect to the clinical criteria of stability; secondly, that reduction of PCT <0.25 and CRP <3 along with clinical stability permit to discriminate within patients with high negative predictive value without subsequent severe complications.

Objective parameters such as these markers to identify safely clinical stability and to determine that the evolution of the patient will not present severe complications would be very useful to clinicians. This information is important to decide subsequent follow-up, sequential treatment and possible discharge. On the one hand, it is well known that if discharge is applied when the patient is unstable, death likelihood is higher.[16,17] It is also known that the time elapsed between reaching clinical stability –a mean of 3 days [2,11,17] – and discharge is what prolongs hospital stay.[18] This prolongation is fundamentally motivated by a conservative or protective attitude facing the possibility of complications arising after stability and the lack of capacity to anticipate them. In fact, a modifiable process of care would be to reduce this time safely for the patient. Although prior studies showed that one day of in-hospital observation is not necessary after stability and switching therapy,[19] some authors reported a non-significant trend towards lower 30-day mortality in the cohort receiving in-hospital observation. This finding and the studies pointing out that a reduction in length of stay was associated with a trend to higher 30 day mortality suggest that clinical benefit of in-hospital observation cannot definitively be ruled out.[20]

Our results show that patients reaching clinical stability within the first 72 hours have significantly initial lower levels of PCT, CRP and cytokines (IL-6 and IL-10). These findings are plausible and support the idea that markers express the degree of systemic inflammation and reflect the response to the resolution of the infection. Thus, high levels of markers and cytokines after 72 hours of treatment are associated with therapeutic failure [1] and with death. [21] Kellum et al [21] have shown that the higher the initial levels of cytokines the worse the prognosis, and that the reduction of cytokines was faster during the first 3 days.[21,22] Interestingly, inflammation persistence after 72 hours has also implications in medium-long-term mortality.[23] Yende et al [23] demonstrated that high levels of IL-6 (mean 6.0) in discharge and, in a lesser degree, of IL 10 (1.2), can increase probability of death in a period comprised between discharge and three months after.

The capacity of CRP to act alone in prediction of severe complications in day 3 reached a diagnostic value similar to clinical criteria, with specificity and positive predictive value (PPV) similar to clinical criteria of stability. In our study, we found that the information of the reduction of systemic inflammation is complementary to clinical stability in ruling out subsequent complications. The study of Halm et al [2] points out that after clinical stability, it is unlikely to present severe complications but progressive ageing of the population, the increase in the number of co-morbidities and of multiple associated treatments (such as steroids) can interfere with the stability parameters. Our study, similarly to that of Halm et al,[2] confirms the high predictive value of the absence of severe complications after reaching stability (3 patients with severe complication of 135, 2.2%), but we found that these 3 patients still presented high levels of CRP and PCT. In fact, the AUC to predict absence of complications of CRP (AUC of 0.77 to 0.84), increases the safety of clinical criteria in the prediction of complications. For the calculation of the threshold of both markers –a non-sufficiently studied objective in the literature– we selected that with a higher specificity and positive predictive value (PPV) of absence of severe complications. Although addition of CRP or PCT to stability criteria only increase slightly their specificity, it is clinically highly relevant since it increases the safety in the prediction for the absence of severe complications.

It is also interesting to analyse the evolution of patients with clinical instability on day 3 but with levels of biological markers under the established cut-off points. Then, the probability of severe complications is also low (2.9% if CRP<3 and 4.9% if PCT <0.25), and lower than if levels of markers remain high. Capelastegui et al [17] analysed that clinical parameters of instability, at discharge, had higher impact on mortality. Then, of the 4 analysed parameters (persistence of fever, systolic blood pressure <90 mmHg, respiratory rate >24 and oxygen
saturation below 90%) detected that persistence of fever presents the higher relationship with mortality and point out that this can be due to a higher systemic inflammation.

The importance of the reduction of the PCT levels has been employed for the calculation of the duration of antibiotics treatment.[6] These studies show that values of PCT under 0.25 can be indicators of treatment suspension. Nevertheless, to our knowledge, there are no studies analysing the levels of markers as stability information in CAP. The perspective of markers as an expression of inflammation is complementary to clinical parameters, alerting the clinician if they remain high, even if clinical stability is reached, and reducing the level of alert if they are lowered. The economic implications of early and safe discharge are enormous.

In conclusion, our results showed that both clinical criteria of stability or reduction of biomarkers after 72 of treatment exhibited a high negative predictive value to rule out subsequent severe complications. Adding biological information provided by CRP and PCT together with clinical criteria of stability improved the safety of that prediction. This information, if confirmed in other studies, would provide very practical and useful information for safe early discharge in hospitalized CAP.
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Figure legend

Figure 1. Graph of biomarkers stratified by clinical stability with or without severe complications appearing after 72 hours.

a- Graph of CRP (in medians).

b- Graph with PCT (in medians).
REFERENCES


Fig 1. a- Graph of CRP medians

Clinical stability with complications after day 3

No clinical stability with complications after day 3

Clinical stability without complications after day 3

Figure 1. b- Graph with PCT medians

Clinical stability with complications after day 3

No clinical stability with complications after day 3

Clinical stability without complications after day 3

No clinical stability without complications after day 3
Stability in community-acquired pneumonia: one step forward with markers?

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