Usefulness of early C-reactive protein kinetics in response and prognostic assessment in infected critically ill patients: an observational retrospective study

A utilidade da cinética precoce da proteína C-reativa para avaliar a resposta e prognóstico nos doentes críticos infectados: um estudo observacional retrospetivo

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Short title: Early CRP kinetics for response and prognostic assessment

Usefulness of early C-reactive protein kinetics in response and prognostic assessment in infected critically ill patients: an observational retrospective study.

**ABSTRACT**

**INTRODUCTION:** The ideal biomarker to assess response and prognostic assessment in the infected critically ill patient is still not available. The aims of our study were to analyze the relationship of early C-reactive protein kinetics with duration and appropriateness of antibiotic therapy and its usefulness to predict mortality in infected critically ill patients.

**MATERIAL AND METHODS:** We have performed an observational retrospective study in a cohort of 60 patients with community-acquired pneumonia, aspiration pneumonia and bacteremia at an Intensive Care Unit. We have collected C-reactive protein consecutive serum levels for 8 days and duration and appropriateness of initial antibiotic therapy. C-reactive protein kinetic groups were defined based on the levels at the days 0, 4 and 7. With a follow-up of one year, we have evaluated mortality at different moments.

**RESULTS:** We have obtained three different C-reactive protein kinetic groups from the sample: fast response, delayed but fast response and delayed and slow response. We have not found statistically significant association between C-reactive protein kinetics and early (Intensive Care Unit, Hospital and 28-days) or late (6 months and 1 year) mortality and antibiotic therapy duration (p>0.05). Although there were no differences statistically significant between the antibiotic therapy appropriateness and the defined groups (p=0.265), no patient with inappropriate antibiotic therapy presented a fast response pattern.

**DISCUSSION:** Several studies suggest the importance of this protein in infection.

**CONCLUSION:** Early C-reactive protein kinetics may not be correlated with response and prognostic assessment in infected critically ill patients. Nevertheless, a fast response pattern trends to exclude initial inappropriate antibiotic therapy.

**KEYWORDS:** C-Reactive Protein, Infection, Kinetics and Mortality.

**RESUMO**

**INTRODUÇÃO:** O biomarcador ideal capaz de avaliar a resposta e prognóstico no doente crítico infetado ainda não está disponível. Os objetivos do nosso estudo foram avaliar a relação da cinética precoce da proteína C-reativa com a duração e apropriação da terapêutica antibiótica e a sua utilidade na predição de mortalidade.

**MATERIAIS E MÉTODOS:** Realizámos um estudo retrospetivo observacional numa coorte de 60 doentes com pneumonia adquirida na comunidade, pneumonia de aspiração e bacteremia numa Unidade de cuidados intensivos. Colhemos níveis séricos de proteína C-reativa durante 8 dias e a duração e apropriação da terapêutica antibiótica inicial. Definimos grupos de cinética de proteína C-reativa com base nos níveis dos dias 0, 4 e 7. Durante um ano de seguimento, analisámos a mortalidade em diferentes momentos.

**RESULTADOS:** Da amostra obtivemos três grupos de cinética de proteína C-reativa: resposta rápida, resposta atrasada mas rápida e resposta atrasada e lenta. Não observamos associação estatisticamente significativa entre a cinética da proteína C-reativa com as mortalidades precoce (Unidade de cuidados intensivos, hospital e aos 28 dias) ou tardia (6 meses e 1 ano) e duração da terapêutica antibiótica (p>0.05). Embora não existam diferenças estatisticamente significativas entre a apropriação da terapêutica antibiótica e os grupos definidos (p=0.265), nenhum doente com terapêutica antibiótica inapropriada apresentou um padrão de resposta rápida.

**DISCUSSÃO:** Vários estudos sugerem a importância desta proteína na infeção

**CONCLUSÃO:** A cinética precoce da proteína C-reativa poderá não estar relacionada com a avaliação da resposta e prognóstico no doente crítico infectado. Porém, um padrão de resposta rápida tende a excluir terapêutica antibiótica inicial inapropriada.

**PALAVRAS-CHAVE:** Proteína C-Reativa, Infeção, Cinética e Prognóstico.

**INTRODUCTION**

More than an half of the patients admitted to an intensive care unit (ICU) are infected. Infection is a major cause of morbidity and mortality in the critically ill patient, being the respiratory focus one of the main infection focus1. Community-acquired pneumonia (CAP) is a major death cause in the western world2 with an estimated mortality rate of 25-40% in patients admitted to the ICU3, 4. Bacteremia is the third cause of infection in the ICU1 with a rate that will probably increase over the time5. Aspiration pneumonia (AP) is also common in ICU, especially in elderly patients6.

As infection etiology is not always determinable, in particular at the beginning of the disease course, empirical antibiotic therapy is adopted based on the patient clinical data. In the critically ill patient, broad spectrum antibiotics are frequently used as an attempt to cover all likely pathogens involved. However, this strategy is associated with higher costs, high risk of side effects and emergence of antimicrobial resistance7. Usefulness of several inflammatory biomarkers to support diagnosis and evaluate therapeutic response and prognosis of infected patients has been largely studied. Nevertheless, the ideal biomarker, combining high sensitivity and high specificity, is not yet available8, 9.

Discovering the ideal biomarker to assess response to antibiotic therapy and to predict outcome in the infected critically ill patient would improve patient management and health care resources allocation.

First discovered and named for its reaction with the pneumococcal C-polysaccharide by Tillet *et al.*10, C-reactive protein (CRP) is a homopentameric acute phase protein with pro and anti-inflammatory properties and is involved in acute immunological responses which make it a pentraxin family member11. Mostly produced in the liver in response to the increase of inflammatory cytokines, in particular interleukin-6, CRP binds to polysaccharides in microorganisms, activating the classical complement pathway of innate immunity[12](#_ENREF_12) promoting activity against the infection as it has been demonstrated previously in mice infected with *Streptococcus pneumoniae*[13](#_ENREF_13). After the stimulus, CRP level rises within 4 to 6 hours, doubles every 8 hours and shows a maximum peak concentration between 36 to 50 hours. When the stimulus is removed, its concentration drops, with a half-life of 19 hours[14](#_ENREF_14). Widely studied as a biomarker, CRP concentration is higher in infected patients compared to patients without infection. CRP concentration above 8.7 mg/dL supports infection diagnosis in patients with a body temperature superior to 38.2°C[15](#_ENREF_15). In a severe infection, CRP reaches values more than ​​1000 times higher the reference value. However, it does not help to establish the infection site[14](#_ENREF_14), [16](#_ENREF_16).

CRP also increases in non-infectious conditions such as autoimmune diseases, malignant tumors, surgeries, trauma, burns, vigorous exercise, heat stroke and also in some psychiatric diseases. However, there are some inflammatory diseases, such as lupus erythematosus, in which CRP remains normal or slightly elevated[14](#_ENREF_14).

Previously, four distinct patterns of CRP ratio as a marker of different responses to antibiotic therapy were proposed: fast, slow, unresponsive and biphasic patterns. They are associated with different prognosis: patients with patterns of fast and slow response apparently have a better outcome compared to patients with unresponsive or biphasic patterns[14](#_ENREF_14), [17](#_ENREF_17).

The main aim of our study was to evaluate the relationship between early CRP kinetics and early and late mortality and antibiotic therapy duration in the critically ill patient. As secondary aim, we evaluate if the antibiotic therapy appropriateness influences the CRP kinetics.

**MATERIALS AND METHODS**

We conducted a single-center retrospective cohort study of patients with CAP, AP or bacteremia admitted in an ICU of Centro Hospitalar Universitário São Joao (CHUSJ), a tertiary hospital in the north of Portugal, from January 1, 2016 to December 31, 2017, with one year of follow-up. CHUSJ’s ethics committee approved the study design.

All patients were 18 years of age or older. We have excluded patients without CRP measurement on day 0 and 4 (both necessary for the classification of kinetic group) or without a minimum of 7 days of follow-up. If CRP measurement on day 7 was necessary for the classification of kinetic group and was not present, the patients were also excluded. Patients with tuberculosis or *Pneumocystis jirovecii* pneumonia, immunosuppression or neutropenia were also excluded. Immunosuppression was considered present if the patient was under short term (daily dose of corticosteroids ≥1 mg/kg or >40 mg of oral prednisolone or equivalent for at least 1 week in the 3 months preceding the ICU admission) or long term (daily dose of ≥0.2 mg/kg prednisolone or equivalent during a minimum of 3 months in the 12 months preceding the ICU admission) corticosteroids use or if, in the prior year to hospital admission, any immunosuppressive therapy (including cytostatics) was used. Neutropenia was defined as an absolute neutrophils count < 1x109/l[18](#_ENREF_18). We have included all eligible patients admitted during the referred period.

Data was collected from the patient clinical process. For the analysis, we included demographic data (age, gender, hospital and ICU admission dates), co-morbidities, microbiological and Simplified Acute Physiology Score (SAPS) II calculated at ICU admission[19](#_ENREF_19). “Accordingly to definitions previously published, the comorbidities recorded were alcoholism, chronic heart failure, chronic kidney failure, chronic liver disease, chronic respiratory failure, diabetes mellitus, drug addiction, human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS), neoplasia, neurological disease or traumatic brain injury. The comorbidities definitions are set out in appendix 1[18](#_ENREF_18).

The diagnosis of CAP, AP and bacteremia were analyzed as mutually exclusive primary diagnosis. CAP was diagnosed when, in addition to suggestive clinical features (e.g. cough, fever, sputum production, pleuritic chest pain), a demonstrable infiltrate was present in chest radiograph or computed tomography scan[20](#_ENREF_20). If this clinical picture was the result of aspiration of either oropharyngeal or gastric contents into the lower airways, it was classified as aspiration pneumonia. Pneumonia was classified as microbiologically documented if a non-skin contaminant microorganism was isolated in blood culture or pleural fluid, urinary antigens were positive for *Legionella pneumophila* or *Streptococcus pneumoniae*, polymerase chain reaction for respiratory virus was positive or if there was a significant bacterial growth of a pathogen in a good lower respiratory tract sample.

Bacteremia was classified as primary if no source was identified or as secondary if an infection source was identified and the same pathogen was simultaneously isolated in blood cultures and the infection site. In addition, bacteremia was classified according to the place of acquisition as community-acquired, hospital-acquired and ICU-acquired. If the infection was diagnosed until the first 48 hours of hospital admission and it was not associated with invasive therapeutic procedures performed in healthcare institutions, we classified as community-acquired bacteremia. If the infection was diagnosed more than 48 hours after hospital admission or clearly associated to invasive therapeutic procedures performed at healthcare institutions we classified as hospital-acquired bacteremia. If it was diagnosed more than 48 hours after ICU admission, we classified as ICU-acquired bacteremia[18](#_ENREF_18). We have decided not to include patients with hospital-acquired pneumonia or ventilator associated pneumonia due to the more subjectivity in defining the moment of infection compared to the others diagnosis.

Initial antibiotic therapy date corresponded to the first day of empirical or directed antibiotic therapy prescribed to one of the three diagnoses established. Empirical antibiotic therapy was defined as antibiotic therapy with no microbiological data. Whenever microbiological documentation and respective antibiogram existed, initial antibiotic therapy was classified as appropriate or inappropriate. Antibiotic therapy was considered appropriate if the bacteria was susceptible *in vitro*, at least, to one antibiotic prescribed in the first 12 hours after presentation. If the bacteria was resistant *in vitro* to all antibiotics prescribed in the first 12h of presentation, antibiotic therapy was classified as inappropriate. In the absence of microbiological documentation, the appropriateness of initial antibiotic therapy was not evaluated[18](#_ENREF_18).Total and appropriate antibiotic duration were collected.

Hospital and ICU length of stay were also recorded as well as the early (ICU, hospital and 28 days) and late (6 months and 1 year) mortality rates.

For the purpose of time-dependent analysis, the first day of antibiotic therapy corresponded to the day 0. The following days were successively defined until day 7. The day 0 corresponded to the first day of the eight CRP values collected. We have collected the highest lactate concentration of the day at days 0, 4 and 7 and which patients have received vasopressor support between D0 and D7.

CRP pattern criteria were established based on the ratio between day 4 and day 0, named initial CRP, and on the ratio of CRP between day 7 and day 0, named late CRP. When an initial CRP ratio was <0.4 was considered a fast response. When an initial CRP ratio was ≥0.8 was considered a delayed and slow response. When initial CRP ratio was ≥0.4 and <0.8, patients were classified according to late CRP ratio: biphasic response if late CRP ratio ≥0.8 and delayed but fast response if <0.8[17](#_ENREF_17), [21](#_ENREF_21). These criteria are set out in appendix 2.

We used IBM SPSS Statistics 25 and RStudio to perform descriptive statistical analysis, using median and interquartile range (p25-p75, IQR) for continuous variables and absolute and relative frequencies for categorical. Continuous variables were compared by Kruskal-Wallis test after testing for normality of distribution and categorical variables by the Fisher’s Exact test. Results were considered statistically significant if p<0.05.

**RESULTS**

“INSERIR TABELA 1 AQUI”

Our sample included 60 patients with a median age of 63.5 (IQR, 46.0-72.3) years (table 1). The majority of the participants were male (n=47; 78.3%), and 42 (70%) had comorbidities. The most frequent comorbidities were diabetes mellitus (28,3%), neoplasia (18.3%), neurological disease/traumatic brain injury (18.3%) and alcoholism (16.7%). The median SAPS II score at ICU admission was 49.0 (IQR, 32.8-65.5) points.

Regarding the infection type, 21 (35%) patients had CAP, 19 (31.7%) had AP and 20 (33.3%) had bacteremia. CAP and AP were microbiologically documented in 57.1% and 78.9% of the cases, respectively. Bacteremia was hospital-acquired in 45% of the episodes, ICU-acquired in 30% and community-acquired in 25%. Most of the cases of bacteremia (80%) were secondary, mainly to intra-abdominal (37.5%) and urological (31.3%) infections.

The highest lactate concentration had a median value of 2.2 (IQR, 1.3-3.1) mmol/l at day 0 (n=52 patients), 1.4 (IQR, 1.1-1.9) mmol/l at day 4 (n= 46 patients) and 1.3 (IQR, 0.9-1.6) mmol/l at day 7 (n= 34 patients). In our sample, 39 (65%) of the patients have received vasopressors during study period.

Antibiotic therapy was empirically started in 53 patients (88.3%) while 7 (11.7%) received initial directed therapy according to antibiogram result. In our cohort, initial antibiotic therapy was appropriated in 83.0% (n=39 patients) of the patients and empirical antibiotic therapy was appropriated in 80.0% (n=32 patients) of the cases according to microbiological data.

The median overall antibiotic therapy duration was 9.0 (IQR, 7.0-14.0) days and while median appropriate antibiotic therapy duration was 10.0 (IQR, 8.0-14.0) days. Median ICU and hospital length of stay were 11.5 (IQR, 6.3-21.8) and 26.5 (IQR, 14.3-43.0) days, respectively.

ICU mortality was 8.3% (n=5 patients) and 12 (20%) died during hospitalization. None of the patients died in the first 8 days after ICU admission. A total of 8 (13.3%) patients died 28 days after admission. At 6 months, mortality was 31.7% (n=19 patients) while after one year mortality rate (n=31 patients) was 51.7%.

CRP serum levels were recorded in all patients at days 0, 4 and 5. In days 1, 2, 3 and 7 we obtained CRP values in 58 patients. CRP serum levels were missing in 4 patients at day 6.

“INSERIR FIGURA 1 AQUI”

CRP time-dependent evolution patterns in response to initial antibiotic therapy are shown in fig. 1 with median tendency line by CRP kinetics groups of the all cohort. Based on the criteria previously defined we have obtained three CRP kinetic groups in our sample: fast response (FR), delayed but fast response (DFR) and delayed and slow response (DSR). We have not found a biphasic response in our sample.

Twelve patients (20%) presented a FR with a median CRP concentration of 233.1 (IQR, 139.7-317.3) mg/L on day 0, of 65.9 (IQR, 38.9-96.2) mg/L on day 4 and of 42.0 (IQR, 14.0-93.0) mg/L on day 7. The 17 (28.3%) patients in the DFR group had a median CRP concentration of 224.9 (IQR, 139.3-290.8) mg/L on day 0, 105.4 (IQR, 76.2-149.0) mg/L on day 4 and 61.0 (IQR, 39.0-86.0) mg/L on day 7. In the DSR group, which included 31 (51.7%) patients, median CRP concentration on day 0 was 73.6 (IQR, 25.8-181.0) mg/L, 146.6 (IQR, 104.4-208.6) mg/L on day 4 and 73.0 (IQR, 40.0-199.0) mg/L on day 7.

When analyzing median CRP concentration evolution in patients with CAP: 1 (4.8%) patient was in the FR group with a CRP concentration value of 71.8 mg/L on day 0, 23.8 mg/L on day 4 and 8.0 mg/L on day 7; 9 (42.9%) were in the DFR group with a CRP concentration of 145.2 (IQR, 98.9-290.8) mg/L on day 0, 102.9 (IQR, 49.4-192.1) mg/L on day 4 and 74.0 (IQR, 39.0 – 162.0) mg/L on day 7; 11 (52.4%) were in the DSR group with a CRP concentration of 64.3 (IQR, 25.8 – 112.8) mg/L on day 0, 126.8 (IQR, 77.4-146.4) on day 4 and 50.0 (IQR, 40.0-156.0) mg/L on day 7.

When analyzing median CRP concentration evolution in patients with AP: in the FR group with a CRP concentration of 149.8 (IQR,118,9-204.9) mg/L on day 0 for 3 (15.8%) patients, 39.0 (IQR, 38.7 – 42.2) on day 4 for 3 (15.8%) patients and 12.0 (IQR, 10.0 – 14.0) mg/L on day 7 for 2 (10.5%) patients; 4 (21.1%) were in the DFR group with a CRP concentration of 228.55 (IQR,166.0-268.1) mg/L on day 0, 112.7 (IQR, 81.2-129.4) mg/L on day 4 and 56.0 (IQR, 42.0 – 64.0) mg/L on day 7; 12 (63.2%) were in the DSR group with a CRP concentration of 52.3 (IQR, 8.65 – 151.15) mg/L on day 0, 164.2 (IQR, 100.8-255.8) mg/L on day 4 and 78.0 (IQR, 40.0-217.0) mg/L on day 7.

When analyzing median CRP concentration evolution in patients with bacteremia: 8 (40%) patients were in the FR group with a CRP concentration of 288.7 (IQR, 205.9-364.8) mg/L on day 0, 90.55 (IQR, 65.9-105.6) mg/L on day 4 and 88.0 (IQR, 34.0-106.0) mg/L on day 7; 4 (20%) were in the DFR group with a CRP concentration of 230.8 (IQR, 215.4-291.0) mg/L on day 0, 109.4 (IQR, 102.5-131.6) on day 4 and 73.0 (IQR, 49.0 – 104.0) mg/L on day 7; in the DSR group with a CRP concentration of 168.8 (IQR, 96.9-212.6) mg/L on day 0 for 8 (20%) patients, 165.1 (IQR, 160.9 – 195.5) on day 4 for 8 (20%) patients and 162.0 (IQR, 37.0 – 203.0) mg/L on day 7 for 7 (35%) patients.

“INSERIR FIGURA 2 AQUI”

CRP time-dependent evolution patterns according to initial appropriate antibiotic therapy are shown in fig. 2 with median tendency line by kinetic CRP groups.

“INSERIR TABELA 2 AQUI”

Mortality rate was evaluated at different time frames during one-year follow-up (table 2). In the ICU, only 1 (8.3%) patient died in the FR group, none of the DFR group of patients died and, in the DSR group, 4 (12.9%) patients died, without statistically significant differences between the groups (p=0.388). At the hospital, in the FR group 1 (8.3%) patient died, in the DFR group 2 (11.8%) patients died and in the DSR group 9 (29.0%) patients died, without statistically significant differences between the groups (p=0.262). After 28 days of the hospital admission, in the FR group 1 (8.3%) patient died, in the DFR group 2 (11.8%) patients died and in the DSR group 5 (16.1%) patients died, without statistically significant differences between the groups (p=0.890). After 6 months of the hospital admission, in the FR group 3 (25.0%) patient died, in the DFR group 6 (35.3%) patients died and in the DSR group 10 (32.3%) patients died, without statistically significant differences between the groups (p=0.873). After one year of the hospital admission, in the FR group 3 (25.0%) patient died, in the DFR group 7 (41.2%) patients died and in the DSR group 11 (35.5%) patients died, without statistically significant differences between the groups (p=0.673).

“INSERIR FIGURA 3 AQUI”

In the fig. 3 we present the total antibiotic therapy duration by kinetics group. The median value of antibiotic therapy duration was 9.5 (IQR, 8.0-16.0) for the FR group, 8.0 (IQR, 7.0-14.0) for the DFR group and 11.0 (IQR, 7.0-14.0) for the DSR group. We have not found statistically significant differences between the kinetics group and the antibiotic therapy duration (p=0.472).

“INSERIR TABELA 3 AQUI”

According to the antibiotic therapy appropriateness (table 3), if initial antibiotic therapy was appropriate, 28.2% (n=11 patients) had a FR, 20.5% (n=8 patients) had DFR and 51.3% (n=20 patients) had DSR. On the opposite, if initial antibiotic therapy was inappropriate, none of the patients had a FR, 37.5% (n=3 patients) had DFR and 62.5% (n=5 patients) had DSR. Nevertheless, no statistically significant difference between the appropriateness of initial antibiotic therapy and the pattern of CRP kinetics was found (p=0.265).

The median value of appropriate antibiotic therapy duration was 10.0 (IQR, 9.0-20.0) for the FR group, 8.5 (IQR, 7.5-12.5) for the DFR group and 11.0 (IQR, 7.5-14.0) for the DSR group We have not found statistically significant differences between the kinetics group and appropriate antibiotic therapy duration (p=0.939).

**DISCUSSION**

CRP kinetics has recently been studied to evaluate response and prognostic in patients in the ICU[22](#_ENREF_22). Our results suggest that there is no relation between the CRP kinetics pattern and both early and late mortality. In the past, several studies have suggested CRP serum levels as a mortality predictor [23](#_ENREF_23), [24](#_ENREF_24), [25](#_ENREF_25).

In ventilator associated pneumonia, a decrease in CRP serum levels after 4 days of antibiotic therapy can predict survival[26](#_ENREF_26), [27](#_ENREF_27). CRP levels on day 3, and mainly on day 5 or 7, compared to admission, provide important prognostic information in CAP patients and may be useful in the assessment of individual clinical evolution [28](#_ENREF_28), [29](#_ENREF_29). The CRP ratio on day 4 of therapy is also an outcome marker in bacteremia of individual clinical course[30](#_ENREF_30). Furthermore, in patients with bacteremia and a SOFA score ≤3 on day 1, a CRP decline ≥ 10% between days 1 and 2 was found to be a good predictor of early clinical stability and low mortality at 30 days. Thus, the decision of a more incisive diagnostic workup and therapy may be due to the CRP non-decrease, while waiting for blood cultures results[31](#_ENREF_31).

In addition, a meta-analysis and systematic review concluded that the weighted mean difference of CRP levels beyond 48 hours was significantly higher in non-survivors when compared to the survivors which suggests that CRP level after 48 hours may be a good outcome predictor in critically ill patients[32](#_ENREF_32).

Our sample with a median SAPS II of 39 predicts an intra-hospitalar mortality of 43.8%. We infer that 65% of our patients had septic shock since they received vasopressor support. However, none of the patients died in the first 8 days and a SMR of 0.45 was documented.

Previously, four different CRP ratio patterns that correlated with the outcome were described. No deaths occurred in the group of patients with CRP ratio pattern of fast and slow response while patients with nonresponse or biphasic response had a worst SOFA score evolution[17](#_ENREF_17).

In our cohort, we only found 3 different CRP kinetics groups. Unlike previous reports, we did not find a statistically significant association between CRP kinetics and early mortality. Some explanations can be raised to justify our results: the small number of patients included, different infection acquisition sites and infection types studied and other clinical conditions or events that may influence CRP kinetics, such as trauma, surgery or source control performance were not taken into account.

We further evaluated the CRP kinetics role in the assessment of late mortality but no significant association was observed.

CRP is routinely used by ICU physicians as an auxiliary criterion for decisions regarding antibiotic therapy. Recently, Oliveira *et al*. demonstrated that serial measurement of CRP can be useful to reduce antibiotic use in septic patients without apparent harm[33](#_ENREF_33). Although single CRP evaluation does not allow the decision of the antibiotic therapy duration in neonatal sepsis, its serial measurement can shorten the period of antibiotic exposure and hospital stay[34-36](#_ENREF_34)(26, 27). Despite being slightly longer in the DSR group, no significant differences in the median duration of total and appropriate antibiotic therapy existed between the 3 groups. This absence of differences may be due to several factors, such as: despite CRP improvement, slow clinical response may prevent ICU physicians to stop antibiotics earlier; some pathogens (e.g., nonfermentative gram-negative bacilli) and infection types (e.g., lung abscess or necrotizing pneumonia) need longer courses of antibiotic therapy; lack of adequate source control (e. g., bacteremia secondary to intra-abdominal sepsis) or the presence of prosthetic material that cannot be removed and ICU physicians do not use CRP kinetics to decide when to stop antibiotic therapy.

The CRP kinetics has also been used to evaluate the appropriateness of initial antibiotic therapy. A fast CRP decrease seems to be associated with appropriate treatment[26](#_ENREF_26) but the best time to asses it has not been defined. In fact, Schmit *et al*, found that an increase in CRP of at least 22 mg/l in the first 48h of antibiotic therapy was associated with ineffective initial antibiotic therapy with moderate sensitivity (77%) and specificity (67%)[37](#_ENREF_37). Other authors observed that, after 3 days of antibiotic treatment, a reduction in CRP ratio <60% was associated with an increased odd of having received inappropriate antibiotic therapy (OR 6.98; 95% confidence interval 1.56-31.33)[21](#_ENREF_21). According to Lisboa *et al*., a CRP ratio of 0.8 at 96h shows a good discriminatory power (area under the receiver operating characteristic curve of 0.86; 95% confidence interval 0.75-0.96) to predict appropriateness of antibiotic therapy[38](#_ENREF_38).

In our cohort, no clear association between CRP kinetics and appropriateness of antibiotic therapy was observed. Nevertheless, most of the patients with FR received initial appropriate antibiotic therapy. On the other side, a delayed decrease in CRP was observed if initial antibiotic therapy was inappropriate. This suggests that CRP ratio on day 4 of antibiotic therapy may play a role in the assessment of initial antibiotic adequacy.

This study has several limitations that may have influenced our results. First, this was a small retrospective observational single center study which may limit the generalization of our results. Second, clinical conditions as well as therapies that could influence CRP kinetics during the course of infection were not analyzed. Third, the retrospective nature of the study did not allow us to compare CRP kinetics with other biomarkers or scores evolution, such as SOFA score, that have also been recommended for the assessment of response to therapy. Finally, CRP value may be higher in patients first admitted to ICU compared to patients admitted to the hospital. This could be justified by the fact that the first patients are in a critical stage with a higher level of inflammatory response when compared to the second group. However, we may not assume completely this affirmation because CRP is influenced by countless situations. For example, the great majority of co-morbidities may raise CRP level. However, there are some that may not rise or even decrease the CRP level.

**CONCLUSIONS**

Our results suggest that the use of CRP ratio kinetics during the first 7 days of antibiotic therapy is not significantly associated with both early and late mortality. Although there was not a statistically significant association between CRP kinetics patterns and antibiotic therapy appropriateness, no patient with inappropriate therapy had a FR CRP pattern. According to our data, we verified that the duration of antibiotic therapy, both total and appropriate, was similar among the different CRP kinetics groups.

Further large prospective studies are needed to clarify and standardize the role of CRP kinetics in response and prognosis assessment in infected critically ill patients.

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**PROTECTION OF HUMANS AND ANIMALS**

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

**DATA CONFIDENTIALITY**

The authors declare having followed the protocols in use at their working center regarding patient’s data publication.

**CONFLICTS OF INTEREST**

All authors report no conflict of interest.

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**LEGENDS**

Table 1 – Main demographic and clinical characteristics of the study sample.

Table 2 – Mortality in the different C-reactive protein kinetic groups.

Table 3 – Antibiotic therapy appropriateness by C-reactive protein kinetic group.

Figure 1 – C-reactive protein time-dependent patterns evolution in response to initial antibiotic therapy with median tendency.

Figure 2 – C-reactive protein time-dependent patterns evolution in response to initial appropriate antibiotic therapy with median tendency.

Figure 3 – Total antibiotic therapy duration by C-reactive protein kinetic groups.