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Patterns of CRP-Ratio Response to Antibiotics - Clinical Implications

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Patterns of CRP-Ratio Response to Antibiotics – An Innovative Concept

After prescription of antibiotics, the evaluation of the patient clinical response as well as the assessment of resolution of the infection relies on the monitoring of the same criteria used for clinical diagnosis. Therefore, following datasuch as temperature, heart rate, respiratory rate, blood pressure, white cell count, and tracheobronchial secretions and chest x-rays is mandatory in an infection like pneumonia (Dennesen et al. 2001; Vidaur et al. 2005). However, chest x-rays, which are fundamental for the diagnosis of pneumonia, have a limited role in the evaluation of clinical response to antibiotics, since an initial deterioration is often expectable and there is commonly a delay in the radiologic improvement. Besides, drugs frequently used in ICU can influence almost all clinical resolution criteria such as steroids, antipyretics or beta-blockers. Consequently, the reliance on those markers may not only result in an inaccurate diagnosis of sepsis but also makes the evaluation of the response to therapy often misleading. To overcome these limitations, physicians frequently use serum biomarkers to assist in their clinical decision making process namely in the assessment of response to antibiotic therapy. C-reactive protein (CRP) is one of these biomarkers and probably the most widely used (Póvoa 2002).

We have shown in different types of infections in critically ill patients, namely ventilator associated pneumonia (VAP), bloodstream infections (BSI), community-acquired pneumonia (CAP), that the course CRP after prescription of antibiotics correlates with clinical course and prognosis (Póvoa et al. 2005). It is possible to monitor absolute CRP changes over time, however we think that the use of relative CRP variations (CRP-ratio) are more informative, since CRP has a first order elimination kinetics. This concept is easily understandable with the following example: an absolute 5 mg/dl decrease in CRP concentration has a different interpretation if the previous level is 50 mg/dl or 10 mg/dl; in the first case CRP concentration dropped 10% in the second CRP decreased 50%. As a result, we have defined the new concept of CRP-ratio has the ratio of each day CRP concentration in relation to day 0 (D0) level to assess the dynamic changes of CRP instead of its absolute values. A sharp decrease in CRP-ratio is a surrogate marker of infection resolution whereas a persistently elevated or an increasing CRP-ratio suggests that infection is refractory to therapy (Póvoa et al. 2005).

Using this concept, CRP-ratio, we introduced another new hypothesis with the definition of four individual patterns of CRP-ratio response to antibiotic therapy:

1. Fast Response Pattern when the CRPratio at D4 of antibiotic therapy was < 0.4 relative to D0 CRP concentration;

2. Slow Response Pattern characterised

by a continuous and slow decrease

of CRP ratio;

3. Nonresponse Pattern when the CRPratio remained always ≥ 0.8 of D0 CRP concentration; and

4. Biphasic Response Pattern characterised by an initial CRP-ratio decrease to levels < 0.8, followed by a

secondary rise to values ≥ 0.8 D0 CRP concentration.

We also showed, in different infections, that these patterns of CRP-ratio response presented a good correlation with the individual clinical course, patient outcome and also with the adequacy of antibiotic therapy.

Patterns of CRP-Ratio Response– Clinical Course and Patient Outcome

Several studies from different groups have confirmed that serial measurements of CRP are useful in the evaluation of clinical course and patient outcome.

In a cohort of severe CAP patients requiring ICU admission (N=53), our group found that CRP-ratio showed a significant and steady decrease in survivors, whereas in nonsurvivors it remained elevated. In survivors, by D3, the CRP-ratio had decreased by almost 50% from the admission CRP concentration. We found that a D3 CRP-ratio > 0.5 was a marker of poor outcome, with a sensitivity of 0.91 and a specificity of 0.55, and was associatedwith the diagnosis of non-resolving severe CAP (Coelho et al. 2008). Besides, the CRP-ratio patterns of response to antibiotics were closely correlated with outcome: 76% of patients with fast and slow response patterns survived, whereas the combined mortality rate of the patients with the nonresponse and biphasic response patterns was 75% (Coelho et al. 2007). We showed similar results in a study with VAP (N=47). All patients with fast and slow response patterns survived, whereas those showing a nonresponse and a biphasic response pattern exhibited a mortality rate of 78% and 75%, respectively.

In BSI, CRP-ratio course was also helpful to predict outcome. In another study by our group (N=44), the timedependent analysis of CRP-ratio, assessed on a daily basis, from D0 to D7, showed a steady and significant decrease in survivors, whereas it remained almost unchanged (or even increased) in nonsurvivors (Póvoa 2005). Those values were already divergent after 24hrs of therapy and become significantly different from D2 onwards. Of the 26 patients with CRP-ratio patterns of fast or slow response, only 2 died, whereas 16 out of 18 patients, with a nonresponse or a biphasic pattern, died. In other words, our group showed that this innovative concept, the patterns of CRP-ratio response to antibiotics, showed a good correlation with individual clinical course in different infectious situations. Those with fast and slow response patterns present a much better prognosis than those with nonresponse or biphasic response pattern.

Seligman et al. analysed 75 VAP patients showing that the decrease of CRP at D4 of antibiotic therapy was predictive of survival, with an odds ratio (OR) of 7.4 (95%CI: 1.58-34.73, p=0.01). In this study, D4 CRP-ratio was also found to be predictive of survival. In survivors, D4 CRPratio was 0.68 whereas in nonsurvivors remained almost unchanged, 0.88.

More recently, in the largest cohort multiple centre observational study assessing biomarkers conducted in 17 Portuguese intensive care units (UCI), a total of 891 patients with community acquired sepsis (CAS) were included and were followed-up during the first five ICU days. In this large study daily CRP-ratio after antibioticprescription was useful, as early as D3, in discriminating CAS patients with good and bad outcomes. A patient with an average decrease of the CRP-ratio of 0.1 per day had 32% more chances of surviving when compared to a patient with the same SAPS II score and the same severity of sepsis but with no decrease of the CRP (CRP-ratio per each 1% change, adjusted OR =1.03, 95% confidence interval: 1.02 - 1.04, p<0.001). Besides, patterns of CRP-ratio response to antibiotics presented a marked correlation with hospital mortality with patients with a nonresponse pattern having a 2.5 times higher probability of dying in comparison with patients with fast response (adjusted OR = 2.5, 95% confidence interval: 1.6 – 4.0, p<0.001) (Póvoa et al. 2010). Slow responders showed a non-significant increase on the odds of mortality in comparison with the fast responders (adjusted OR = 1.5, 95% confidence interval: 0.9 – 2.5, p=0.124). By D3, median CRP-ratio (5th and 95th percentiles) was 0.81 (0.40, 1.30), 0.95 (0.62, 1.48) and 1.22 (0.70, 6.64) in patients with fast response, slow response, nonresponse patterns respectively (p<0.001).

In all these studies, the patterns of CRPratio response allowed the early identification, between D3 and D4, of patients with poor response to antibiotics and consequently with poor prognosis (Table 1). Thus, the recognition of the patterns of CRP-ratio in clinical practice may significantly influence the clinical decision making process. In patients with persistently elevated or rising CRP-ratio, that is nonresponse or biphasic response patterns, an aggressive diagnostic and therapeutic approach should be attempted in order to prevent further clinical deterioration and to diagnose potential infectious complications related or not to the primary infection, like an empyema, an acalculous cholecystitis, appendicitis or a catheter-related bloodstream infection in the case of a pneumonia.

In opposition, patients with consistent CRP-ratio decrease, patterns of fast and slow response, usually have an adequate antibiotic therapy, resolution of infection and good prognosis. As a result, these patterns could be used in conjunction with the clinical evaluation to tailor the duration of antibiotic therapy.

Patterns of CRP-Ratio Response and Adequacy of Antibiotic Therapy

The impact of initial adequacy of antibiotic therapy on mortality has been repeatedly demonstrated and in addition a late antibiotic escalation, from inadequate to adequate antimicrobials seems to have little impact on survival (Iregui et al. 2002).

In a population of 68 VAP patients, Lisboa et al. found a good correlation between the bacterial burden (measured by quantitative tracheal aspirates) and CRP levels. In addition, in patients with adequate antibiotic therapy, CRP-ratio by D4 fall to 0.58±0.32 while, in patients with inadequate therapy, CRP-ratio eventually rise to 1.36±1.11. Besides, authors found a correlation between bacterial load in serial tracheal aspirates, CRP-ratio and the adequacy of antibiotic therapy. By day 4 of antibiotic therapy, patients with adequate antibiotics showed a fall in the

bacterial load and CRP-ratio (D4 CRP-ratio – 0.58) whereas in those with inadequate therapy was the opposite, bacterial load remained elevated as well as CRP-ratio (D4 CRP-ratio – 1.36, $p<0.05$). As a result, we could speculate that patients with adequate antibiotic therapy are those with a fall in the microbiological burden and consequently with a decrease in the inflammatory response. Consequently, the fall of CRP-ratio could be a surrogate marker of this response with a good correlation between CRP-ratio and the change in microbiological burden. In patients with inadequate antibiotic therapy we would expect an opposite behaviour. The authors concluded that serum CRP-ratio variation was a quick and objective surrogate for bacterial burden and inflammation. Besides the authors found in this study, a strong association between CRP-ratio and survival was perceived (CRP-ratio: 0.68 ± 0.39 in survivors and 1.35 ± 1.33 in nonsurvivors) (Lisboa et al. 2008).

Bruns et al., in a cohort of 137 patients with severe CAP found that patients treated with inappropriate empirical antibiotics had significantly slower normalisation of CRP levels measured in the first three days and in the first week of hospitalisation. In multivariate analysis a decline of <0.6 in CRP-ratio levels in three days and a decline of <0.9 in CRP-ratio levels in seven days were both associated with an increased risk of having received inappropriate empirical antibiotic treatment (Bruns et al. 2008).

In a cohort of 47 patients with microbiological documented VAP (Póvoa et al. 2005), those with initially adequate antibiotic therapy exhibited a better outcome than did those with initially inadequate therapy. The overall mortality rate was 18.4% in the 38 patients with adequate antibiotics and 66.7% in the nine patients with inadequate antibiotic therapy. Also, patients who initially received adequate antibiotics showed a significant CRP-ratio decrease (0.6 at D4) in comparison with those with inadequate therapy (>1.0 at D4, $p<0.001$). In this study, all patients with a pattern of fast response received adequate therapy, as well as 85% of the patients with a slow response. Conversely, 44% of the patients showing a nonresponse pattern and 25% with a pattern of biphasic response received inadequate antibiotic therapy. In other words, the patterns of CRP-ratio response are also markedly influenced by the adequacy of empiric antibiotic therapy.

We found similar results in a cohort of 44 patients with BSI. In this study the mortality was significantly higher among patients initially treated with inadequate therapy (76.9% vs 25.8%, $p=0.002$). Patients who initially received adequate therapy had a marked CRP-ratio decrease, compared with patients who initially received inadequate therapy (Póvoa et al. 2005).

Altogether, these results demonstrate that CRP-ratio can be an important marker in the early identification of patients who had initial inadequate antibiotic therapy. The recognition of the individual pattern of CRP-ratio response to antibiotic therapy reflects not only the infection response but in addition is useful in the assessment

of the adequacy of antibiotic therapy. Consequently, this innovative concept, patterns of CRP-ratio response, seems to be a crucial tool in the decision to modify early the antibiotic treatment in patients with patterns of non-response or a biphasic response, or allow the shortening of antibiotic treatment in patients with rapid-response pattern.

Conclusion

This innovative concept, introduced by our group in 2005, has been repeatedly confirmed by different groups, in different countries and in different infections. The relative changes of CRP, CRP-ratio, as well as the patterns of response show a good correlation with clinical outcome, mortality and the adequacy of antibiotic therapy.

We suggest that in patients showing the patterns of nonresponse and biphasic response, with these easily available and inexpensive tools, we should follow an aggressive diagnostic and therapeutic approach to prevent further clinical worsening trying to change the associated ominous prognosis. Also, the identification of fast and slow CRP-ratio patterns of response may help to reduce the length of antibiotic therapy, as well as to reduce the risks of emergence of resistant strains and costs of medication.

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