C-reactive protein and procalcitonin in the assessment of infection response to antibiotic therapy

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Definite diagnosis of infection requires microbiological documentation; however, the identification of a specific etiology is frequently missing. In addition, bacterial cultures require at least 24-48 hours for a final result, which is too long for a decision to start antibiotics.

Currently, the evaluation of the infection response to antibiotic therapy relies on the resolution of the same criteria used in the diagnosis. However, the clinical parameters used in the diagnosis can be influenced by a number of non-infectious factors.

With these limitations, researchers and clinicians look at the inflammatory cascade for a potential objective serum marker of infection. By definition a serum marker should be absent if the patient is not infected, appear concomitantly and ideally precede the clinical manifestations of infection, disappear with successful therapy or remain elevated if infection is refractory to treatment.

Serial measurements of biomarkers, namely CRP and PCT, used in combination with the clinical examination are very useful in the monitoring of infection response to antibiotics.

Introduction

After diagnosis of infection and prescription of antibiotics the assessment of clinical response is based essentially on clinical and eventually on microbiological criteria, mostly the same used in diagnosis [1].

However, clinical parameters can be influenced by a number of non-infectious factors, like the drugs used in critical care settings [2].

Moreover, microbiological criteria are of little help because of the delay of culture results, the interference of antibiotics with bacterial growth in vitro and the difficulties in obtaining some microbiological samples (e.g. from cerebrospinal fluid or peritoneum).

On the other hand, treatment failure may be wrongly presumed in the presence of a slow improvement or the appearance of a superimposed problem, such as drug fever, inflammatory conditions or a new hospital-acquired infection [3].

In this context, the use of serum markers, namely C-reactive protein (CRP) and procalcitonin (PCT), has been shown to help in the assessment of response to therapy, and thereby contribute to the clinical decision [4].

Characteristics of an infection biomarker

By definition, a marker of infection should be absent if the patient is not infected, facilitating the differentiation between infectious and non-infectious causes of inflammation, and it should appear concomitantly and ideally precede the clinical manifestations of the infection and disappear with successful therapy or remain elevated if infection is refractory to treatment [5].

Besides its concentration, changes over time should be rapid enough, not more than 24 hours, for a useful real-time interpretation [4]. A risk factor for infection is a sign that identifies a group of patients at risk of developing an infection in the future.

Finally, a mediator is an event state, substance or process that causes the disease and that is present during some or all of the clinical expressions of the disease [5].
Ideally, an infection or sepsis marker should meet the following requirements [5, 6]:

- Easy to use and interpret
- Rapid and reproducible test
- Dynamic (rapid increases and decreases)
- Reflect the effectiveness of antimicrobial treatment and other measures of source control (more accurately than conventional clinical and laboratory signs)
- Have high sensitivity and specificity, easy handling and interpretation
- Shorten the time to and improve the diagnosis
- Not be modified by any treatment or intervention unless related to the source control and/or antibiotic therapy
- Allow the differentiation between underlying viral and bacterial infections
- Have a good correlation with clinical severity and mortality
- Have low costs and be rapidly available
- Exhibit large amplitude of variation and have a non-"exhaustion" or "fatigue" behavior in prolonged septic episodes (to evaluate the clinical response)

Serum biomarkers in the evaluation of infection response to antibiotics

Serum CRP is an acute-phase protein exclusively synthesized by the liver largely under transcriptional control of IL-6. CRP levels rise rapidly in response to several inflammatory stimuli, bacterial infection being one of the most potent.

The secretion of CRP begins within 4-6 hours of the stimulus, doubling every 8 hours and peaking at 36-50 hours. With a very intense stimulus, the CRP concentration can rise above 500 mg/L, i.e. more than 1000 times the reference value.

After the disappearance or removal of the stimulus, the CRP concentration decreases rapidly with a half-life of 19 hours. CRP can remain elevated, even for very long periods, if the underlying cause of the elevation persists; its serum concentration only depends on the intensity of the stimulus and on the rate of synthesis.

Only interventions that affect the inflammatory process responsible for the acute-phase reaction influence CRP level.

Moreover, CRP has a large amplitude of variation, which is easily detected by routine laboratory methods, and it is possible to identify a clear threshold for the diagnosis of acute inflammation, especially infection.

It is also possible to define, according to CRP evolution, its daily ratio, i.e. the daily concentration of CRP divided by its initial concentration (measured on the day of the diagnosis of infection and the start of therapy).

A decreasing ratio of CRP correlates with infection resolution and can be more meaningful than the absolute daily CRP level itself.

We were able to show that this relative variation of CRP concentrations correlated with the patient outcome. Using the CRP ratio we were allowed to identify four different patterns of CRP response to therapy [2, 7].

The first, a fast response pattern, consists of a rapid decline of the CRP ratio to less than 0.4 by day 4. The second, a slow response pattern, is characterized by a continuous decline of the CRP ratio, its value by day 4 being less than 0.8 (but more than 0.4).

The third is a non-response pattern, which is defined by a CRP ratio course persistently above 0.8 (and sometimes even increasing), and the last, a biphasic response pattern characterized by an initial drop of the CRP ratio below 0.8 followed by a secondary rise to a value above that threshold.

In a study of our group, 47 documented ventilator-associated pneumonia (VAP) patients [2] were classified according to these CRP patterns. None of the 30 patients with one of the two first described CRP ratio decreasing patterns died, whereas only four of the 17 patients with persistently elevated CRP levels survived ($p < 0.001$).

Apart from this correlation with prognosis, we found that CRP kinetics also correlated with the adequacy of initial antibiotic therapy: those with an adequate empiric antibiotic therapy showed a marked drop in CRP ratio, whilst in patients with inadequate antibiotics the CRP ratio was always above 1.0.

Using the same methodology, we obtained similar findings in 44 patients with bloodstream infections [7].

We also found in patients with severe community-acquired pneumonia (CAP) a correlation between CRP ratio and outcome [8]. Failure to decrease the CRP ratio to less than 0.5 by day 3 of therapy was predictive of a bad outcome. Moreover, in this study a decline of more than 31 % of CRP levels in 2 consecutive days predicted recovery (of 29 patients with this finding, 27 survived).

Similarly, in a 28 CAP inpatient population a sharp decrease in CRP ratio (to less than 0.32) after 96 hours of therapy was noted [9]. All the four patients considered to be antibiotic failures had persistently elevated CRP ratios.

Lisboa et al. evaluated in 68 monomicrobial VAP patients not only CRP ratio but also its correlation with microbiological burden (measured by quantitative tracheal aspirates) [10].

In patients with adequate antibiotic therapy, the CRP ratio at day 4 dropped to 0.58 (± 0.32) while, with inadequate antimicrobial therapy, the CRP ratio eventually rose (1.36 ± 1.11), as we have already pointed out [2].

Interestingly, these changes in CRP ratio correlate with changes in bacterial load, which also stayed high in patients with inadequate antibiotic therapy. That is to say, the resolution of the infection, assessed by the changes in bacterial burden, paralleled the resolution of the inflammatory response measured by a surrogate marker, CRP.

No study was accomplished to evaluate the performance of CRP ratio within the first 2 days of therapy. However, its serial measurements may provide some degree of confidence that antibiotics are adequate (or not) well before the culture results are made available.

However, even in patients with microbiological identification, a lack of a decreasing CRP ratio may provide information about an ongoing complication (like endocarditis or an abscess) or another hidden infection [11].

Therefore, in high-risk patients (especially in septic shock), with a high SOFA score, failure to reduce the CRP ratio as early as the second day of antibiotic therapy should prompt an aggressive diagnostic and therapeutic approach, with source control efforts (e.g. removing central lines, debriding necrotic tissue) and

performance of a full diagnostic approach (e.g. repeating microbiological cultures, performing ultrasound or CT scan).

Additionally, the enlargement of the antibiotic spectrum should also be considered to prevent further clinical deterioration, as these patients are at a very high risk of death. However, it should be noted that no study has yet been done assessing the value of changing therapy (or other therapeutic approach) based on CRP serum values.

The value of PCT kinetics was also assessed in a population with documented VAP. A good correlation with clinical severity was found [12].

However, some patients with microbiologically proven VAP presented undetectable PCT levels at the day of diagnosis and, as a result, in these patients PCT relative variations could not be used to monitor response.

In another study PCT was proposed to diagnose and guide the duration of antibiotic therapy in CAP. Patients in the PCT-guided group reduced their antibiotic therapy to 5 days, compared with 12 days in patients treated according to the guidelines [13].

However, an almost undetectable level of PCT on the day of diagnosis was also found in 29 % of these patients. Consequently, in those patients, it was virtually impossible to evaluate the rate of PCT decline.

In 75 VAP patients the decrease of both PCT and CRP at day 4 of therapy was predictive of survival, with odds-ratio of 4.4 and 7.4, respectively [14]. In that study the CRP ratio at day 4 of therapy was 0.67 for survivors and 0.88 for non-survivors.

To overcome the limitations of a single biomarker, some studies evaluated the relative accuracy of panels of biomarkers. Gaini *et al.* evaluated the accuracy of four biomarkers in 194 patients, including CRP and PCT, to identify patients with infection [15].

They found that CRP was the biomarker with the highest diagnostic performance, whereas PCT presented the lowest (AUC = 0.83 vs. 0.77, respectively).

Another unsolved issue is the optimum duration of antibiotic therapy. Eventually it should vary with the severity of the infection as well as with its clinical course. Serum markers may help identify patients who can benefit from a short antibiotic course.

In a 425 neonatal pediatric population CRP was used to define length of therapy: its peak levels were used to define the duration of treatment and its normalization was used to stop antibiotics [16]. Only 19 patients received antibiotics for more than 5 days and there was no readmission within a month.

Conclusion

Neither CRP nor PCT are the perfect marker of infection, since a variety of non-infectious conditions can increase their concentrations. However, the interpretation of non-infectious causes of CRP and PCT elevations are usually straightforward.

On the contrary, infection, especially in critically ill patients, can present a diagnostic challenge. As a result CRP and PCT elevations without an obvious cause should prompt the search for an infection.

The use of serial CRP determinations is useful in monitoring therapeutic response of serious infection, allowing early identification of complications or antibiotic failures.

Therefore this strategy may help improve infection therapy, helping the clinician to start antibiotics sooner, reduce the duration of its course, rapidly assess its adequacy and also prevent non-infected patients from being exposed to these drugs.

On the other hand, PCT seems to be less sensitive to the diagnosis but a better indicator of the severity of an illness and its prognosis.

Notwithstanding, the use of serum markers will always

be a complementary diagnostic tool since the diagnosis of bacterial infections will continue to require a thorough clinical evaluation and adequate cultures.

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