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The Role of C-Reactive Protein in Guiding Antibiotic Therapy: Is it Worth it?

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Abstract

The management of bacterial infections in hospitalized patients is a challenge in clinical practice and the decision-making process for initiating or discontinuing antimicrobial therapy is one of the main axes of this medical condition. This mini-review outlines the ideal features of an effective and safe circulating biomarker and provides valuable insights into the role of C-Reactive Protein (CRP) in the care of patients with suspected or confirmed bacterial infections, including those admitted to intensive care units. Furthermore, we highlight the importance of early intervention and appropriate antimicrobial use in this population and present some comparative data on Procalcitonin (PCT) and CRP as biomarkers to guide antibiotic therapy in hospitalized patients with bacterial infections.

Keywords: Adult; C-Reactive Protein (CRP); Procalcitonin (PCT); Antimicrobial agents; Duration of antibiotic therapy; Biomarkers

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; CRP: C-Reactive Protein; DeCS: Health Sciences Descriptors; Emtree: Embase Subject Headings; ER: Emergency Room; ICU: Intensive Care Unit; IL-1: Interleukin-1; IL-6L Interleukin-6; MeSH: Medical Subject Headings; PCT: Procalcitonin; SOFA score: Sequential Organ Failure Assessment score; TNFα: Tumor Necrosis Factor Alpha

Introduction

The management of hospitalized patients with bacterial infections has always been a challenge in clinical practice. The decision upon when is the proper time to start, de-escalating or removing an antimicrobial drug depends on several factors including clinical response, presence or absence of fever, microbiological documentation and improvement of both imaging and laboratory test results. This timing is crucial not only to address a sustained response against the pathogens and therefore improve clinical outcomes but also to rationalize the use of antimicrobials and therefore reduce the development of bacterial resistance against these essential drugs [1].

Throughout the years, physicians have tried to establish protocols to guide their practice with biomarkers that could predict the appropriate moment to start and discontinue antimicrobial therapy. Several molecules were assessed, but the most important ones were C-Reactive Protein (CRP) and Procalcitonin (PCT). Despite the efforts, we still are not able to support the use of a single biomarker protocol or even a combination of them to guide antibiotic therapy or to predict and assess clinical response. In this mini-review, we discuss the usefulness of CRP in the context of bacterial infections and its worth as a worldwide available, low-cost lab test to help doctors with diagnosis and clinical decisions, such as the timing of de-escalating and interrupting antimicrobial treatment [2].

Literature Review

This review is based on a recent article published by our group elsewhere. Additionally, we performed an independent search for further evidence in MEDLINE (PubMed interface), Scopus and SciELO databases. Search strategies included medical subject heading terms such as: C-reactive protein, antibiotic therapy, adults, antimicrobial therapy, antibacterial agents, circulating biomarkers, duration of therapy and free days of antibiotic. The search emphasized recent articles, published case series, consensus statements, guidelines, meta-analyses, systematic reviews and prospective cohort studies, critically reviewed and selected by the authors [3].

What is and why do we use circulating biomarkers in clinical practice?

Circulating biomarkers are molecules present in the bloodstream that may be related to or are the result of an abnormal metabolic or infectious process. To a larger or smaller extent, these substances can help in the diagnosis, monitoring of treatment, or prognosis of patients with suspected infections. According to the surviving sepsis campaign guidelines, the main functions of a biomarker in a clinical setting of severe infection is to help clinicians to:

- Determine the likelihood of the current process being infectious.
- Detect the severity of the infectious process and the risk of deterioration to septic shock.
- Identify the most likely pathogens.
- Assess the clinical response of the patient.

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- Recognize when antibiotics can be safely interrupted.

In this context, researchers have struggled to find evidence of the use of biomarkers as a guide to provide individualization of treatment protocols, such as starting or discontinuing antimicrobial therapy. Currently, none of the studied biomarkers are recommended solely as a protocol for diagnosis and prognosis in sepsis, since they do not provide a reliable prediction of clinical outcomes. Above all, in hospitalized patients, mostly in those with infection-related acute organ dysfunction, no biomarker seems to be sufficiently accurate to guide the decision of starting or not an antimicrobial treatment, even though several studies suggest that C-reactive protein and mostly procalcitonin are potentially useful to guide the discontinuation of these drugs [4].

The rationale for early discontinuation of antibiotic therapy

In 2021, WHO announced antimicrobial resistance as one of the top ten global public health threats facing humanity within the next decades. The reduction of the over prescription of antimicrobials must be accomplished as a goal of best practices worldwide, as we faced a concerning emergence and spread of multidrug-resistant pathogens in the last century. In addition, with more judicious antibiotics prescription, we can offer cheaper and safer medicine, since treatment expenses, adverse effects, risk of secondary infections, recurrence of infections, mortality rate and interference with the microbiome are all reduced. Indeed, in a meta-analysis carried out by Royer, Stephanie et al., the authors analyzed the safety of short versus long courses of antimicrobial therapy in different bacterial clinical scenarios, including pneumonia, urinary tract and intra-abdominal infections. They found no significant statistical difference in the clinical and microbiologic cure, recurrence of infection and mortality between the two groups, strengthening the current trend of early discontinuation of antibiotic therapy and shorter periods of antibiotic exposure [5].

What are the ideal features of a biomarker?

The main utility of a biomarker in infectious processes, including sepsis, are prediction, diagnosis, assessment of therapy-response and guidance of antibiotic therapy, which is further divided into prognostic, predictive and theranostic. As the ideal features of a biomarker are highly tied to its intrinsic properties and its final use, their optimal characteristics in this scope are:

- An elevation during sepsis.
- Positive correlation with the severity of the presentation or dysfunction.
- Prolonged serologic persistence.
- Enabling an early diagnosis by a rapid, accurate and bedside measurement.
- To be minimally invasive.
- Prediction of course and prognosis, response to therapy and facilitating therapeutic decisions.

In analytical terms, some characteristics are accessibility in routine use, availability, reproducibility, accuracy and cost-effectiveness. It should also have good sensitivity and specificity, with high predictive values, be objective, easily interpreted and with as little concomitant therapy or disease confounder as possible. The biomarkers, each with their specific uses and limitations, provide additional valuable information on three main axes: The host systemic manifestations, the severity of organ dysfunction and microbiologic documentation [6].

In order to use a biomarker for host response and degree of organ dysfunction, some features to be considered are its intrinsic properties, its biological source, it’s time to increase after insult and until peak concentration and its half-life. Other essential factors that interfere importantly are possible confounders, such as the use of steroids or immune suppressors, neutropenia, renal failure or renal replacement therapy, chronic, acute liver failure, secondary infection and its difference in bacterial and viral infections.

Microbiologic documentation includes pathogen-specific biomarkers, such as respiratory or urinary antigen tests for influenza, SARS-CoV-2 or *Streptococcus pneumonia*, which are usually highly specific but have low to moderate sensitivity, and have a low negative predictive value, not being reliable as a rule-out test. A few combined methods, such as Glutamate Dehydrogenase (GDH) and free toxins A and B for *Clostridioides difficile* Infection (CDI), may elevate their specificity and sensitivity, especially in cases of low predictive values due to low CDI prevalence. Another ideal use of pathogen-specific biomarkers would be guided algorithms, such as those investigated in two RCTs that assessed the discontinuation of empirical antifungal therapy in critically ill patients through (1,3)-β-D-glucan-guided strategy. Therefore, larger studies to determine and standardize specific biomarkers for bacterial infections are necessary and promising and should be encouraged in the future to provide new algorithms for clinical practice [7].

C-reactive protein and the decision for commencing, de-escalating and interrupting antimicrobial therapy

To our knowledge, there is no established protocol that defines the exact moment in which antimicrobial therapy should be started, altered or ceased based on a sole laboratory test. This decision depends on several factors including the patient's clinical status, the primary diagnosis, the source of infection, the natural history of the disease, biochemical dynamics (lab tests) and imaging exams. The current surviving sepsis campaign establishes the start of antibiotic therapy within one to three hours after the suspicion of sepsis, depending on whether this diagnosis is more or less probable. It is known, however, that this task is not easy to be performed in clinical practice, with some studies demonstrating ill patients awaiting their antibiotics for more than one hour in several hospital facilities. The decision to start an antibiotic treatment must be supported by reasonable clinical grounds and followed by a daily revaluation. In this context, the initiative of “watch and wait” proposed by Denny et al., is noteworthy and seems to be useful, reserving antibiotics for patients with proven bacterial infection and/or with a clinical presentation consistent with life-threatening infection and/or hypotension due to suspected infection [8].

CRP levels have been demonstrated to be directly associated with mortality in critically ill patients, with high levels associated with higher morbidity. In this context, we could use CRP as an ancillary parameter to start antibiotic therapy in patients with suspected infection. Most interestingly, a significant reduction of CRP concentration is associated with a better prognosis, suggesting that this marker could aid in the decision regarding antibiotic discontinuation. During the last few years, some single trials have demonstrated that CRP allows a reduction of the duration of antibiotic therapy without apparent harm in hospitalized patients with infection, including those severely ill. According to these studies' protocols, other important factors to consider before ceasing antimicrobial therapy are:

- Clinical improvement.
- Absence of fever for at least 48-72 hours without the use of antipyretics.
- Improvement or resolution of organic dysfunctions related to infection.
- Radiological improvement (if applicable).

Figure 1 summarizes how CRP can be used as a guide to manage antimicrobial therapy in critically ill patients. Despite promising, severe patients that persist with high serum levels of CRP, even after a complete course of antimicrobials, are still difficult to manage. Identification of occult infectious sources and isolation of multidrug-resistant pathogens or polymicrobial infections is crucial to appropriate management. Moreover, a substantial number of these patients have resolved the infectious process, which makes it necessary to search for alternative reasons to explain the persistently elevated CRP levels. Maintaining antibiotic therapy in these cases might be counterproductive and probably detrimental [9].

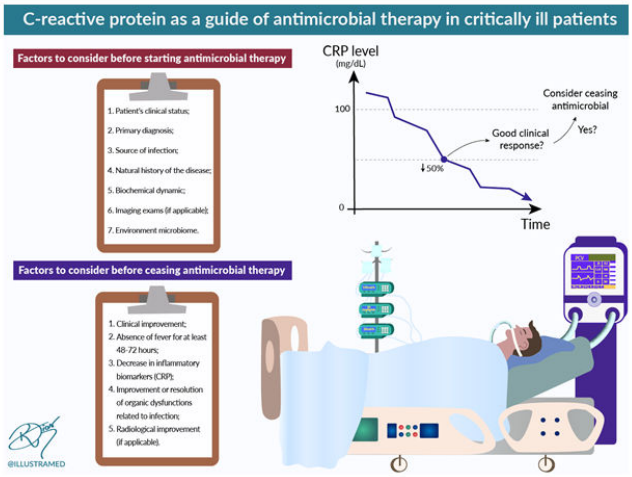

Figure 1: C-reactive protein as a guide of antimicrobial therapy in critically ill patients.

The relationship between dropping levels of CRP and a better prognosis may help clinicians decide to de-escalate or even interrupt antibiotic therapy in critically ill patients with suspicion of bacterial infection, after considering several factors such as clinical status, primary diagnosis, source of infection, the natural history of the disease, biochemical dynamic, imaging exams (if applicable) and environment microbiome [10].

C-Reactive protein and procalcitonin: Pros and cons

CRP is a member of acute phase reactants proteins that play an essential role in innate immune system responses. Apoptosis clearance, phagocytosis and complement binding are all CRP-dependent processes that can only occur after its release from hepatocytes in an intensely stimulated pro-inflammatory environment modeled by cytokines, such as IL-1, IL-6 and TNFα. Sepsis, trauma, surgery, necrosis and autoimmune conditions are all causes of CRP increase due to the above-mentioned mechanism. CRP plasmatic levels are determined by the synthesis rate, which is directly associated with the intensity of the inflammatory insult and once the primary stimulus is removed, its levels start to decrease with elimination following a half-life pattern of 19 hours. One of the advantages is that CRP levels are not influenced by the most common confounding factors, which are renal failure or renal replacement therapy, immunosuppression or neutropenia and they do not differ between individuals with or without cirrhosis. In addition, other advantages are its reliable, stable, reproducible, rapid and inexpensive measurement [11].

Knowing that the primary function of CRP is host defense against bacteria, this biomarker is sensitive to infections. However, due to its raised levels in inflammatory processes, including postoperative periods and neoplasms, CRP is not specific. Therefore, despite CRP's high sensibility, ranging from 78% to 90%, its specificity for diagnosing infectious acute infectious processes is low, ranging from 42%-61% in different studies [12].

PCT is a peptide formed by 116 amino acids with a molecular weight of 13 kDa, derived from pre-procalcitonin which is synthesized mainly by thyroid C-cells, despite the extra-thyroid production by other organs and within leukocytes. PCT is converted into calcitonin after the activity of the enzyme prohormone convertase. Physiologically, PCT is barely present in the bloodstream. During inflammation, however, proinflammatory cytokines can raise PCT levels up to 100-1000-fold. After the stimulus, PCT increases its values 3-4 hours after the insult with a half-life of 24 h [13].

Two meta-analyses and two cochrane reviews indicated that PCT-guided therapy reduced the duration of antibiotic use without compromising clinical success or increasing mortality. The cost-effectiveness of PCT use in this context is still a matter of debate, being also necessary to consider its limited availability in low and middle-income countries. In addition, another disadvantage of PCT use is the confounder factors since it is not reliable to assess immune-compromised, neutropenic patients and those with renal failure or in a protocol of renal replacement therapy.

Finally, three RCTs found that PCT-guided protocols have no impact on short-term mortality, length of ICU stays or hospitalization. Currently, surviving sepsis guidelines recommend against the use of PCT to guide antibiotic therapy, due to the insufficient evidence that supports its beneficial, safe and cost-effective use.

Discussion

Should we use C-reactive protein to guide antibiotic therapy?

CRP is well-established and is continuously studied for discontinuation of antibiotic therapy and therapeutic response, mainly in the secondary and tertiary settings, being used for critically ill septic adult and pediatric patients and the general population as well. However, the use of CRP as ancillary information to aid in the decision-making for antibiotic discontinuation is usually made in a non-protocolized manner. In a recent systematic review and meta-analysis of our group, a CRP-guided strategy effectively reduced the duration of antimicrobial therapy in hospitalized patients with acute bacterial infections, without apparent harm. Interestingly, the studies included in this review applied pre-specified protocols with clearly defined cut-offs of PCR reduction. However, the number of studies testing the role of CRP to guide antibiotic discontinuation is remarkably low. Moreover, these predominantly single-center trials enrolled small samples of patients.

Borges et al., ran an RCT that tested a CRP-based protocol to guide antibiotic discontinuation among ICU patients, using pre-specified criteria that included a reduction in this biomarker's levels and data regarding clinical (including SOFA score) and microbiological response to the treatment. Patients enrolled in the experimental arm were reassessed after three or five full days of antibiotic therapy, according to their baseline CRP levels, *i.e.*, above or under 100 mg/L. Daily CRP measurement was maintained and antibiotics were stopped when CRP levels decreased over 50% or on day 7, in case of a favorable clinical response. In patients with baseline CRP levels under 100 mg/L, the antibiotic therapy was discontinued after three days of treatment if there were no signs of active infection, the SOFA score decreased, and CRP levels were under <35 mg/L. When those criteria were not met, a daily CRP measurement was maintained, and antibiotics were stopped when CRP decreased under 35 mg/L or on day 7. The duration of antibiotic therapy in the control group followed the best evidence available in the literature. Hence, this study supported that the daily monitoring of serum CRP and the set of cut-offs for the reduction in this biomarker's levels may allow early discontinuation of antibiotic therapy.

In 2013, Oliveira et al. carried out an RCT to compare the efficacy of CRP and PCT as circulating biomarkers to guide the antibiotic therapy among 91 critically-ill patients with suspected or confirmed bacterial infections with both CRP and PCT protocols ensuring at least seven days of full antibiotic therapy. The mean duration of antibiotic therapy was seven days among patients treated according to the PCT-guided protocol and six days in those enrolled in the CRP group, without significant benefit of one marker over another. Despite suggesting a similar efficacy of both biomarkers, this study has the limitation of lacking a control group of non-biomarker-guided antibiotic therapy.

More recently, a study conducted in 3 tertiary care hospitals in Geneva, Lausanne, and St Gallen, Switzerland, included 504 patients randomized on day five of treatment against gram-negative bacteria infections. As the main results, the authors found that fixed protocols of seven or fourteen-day antimicrobial treatments were non-inferior to the CRP-guided antibiotic therapy, regarding both efficacy and safety endpoints.

CRP absolute values and its progression during hospitalization also reflect the response to therapy and the increase of CRP-ratio (CRP-value of day 0/CRP-value of day analyzed) suggests that the current infectious process is non-responsive to therapy, being a valuable marker of sepsis resolution or failure of treatment. Further research is necessary to fully validate CRP as a guide in antibiotic therapies and especially in the early discontinuation of antimicrobials in hospitalized patients. Also, it should be emphasized that many patients with persistently elevated CRP levels have underline or acute non-infectious conditions and might not benefit from prolonged antimicrobial courses. CRP remains a promising biomarker that may add to the efforts to reduce inappropriate antimicrobial exposure and its deleterious consequences.

Conclusion

We reviewed herein the main aspects that we seek on a biomarker to guide antimicrobial therapy in hospitalized patients and the reasons why we believe CRP is useful in this setting. Despite the shortage of solid evidence to support a CRP-based protocol to guide antibiotic therapy duration in hospitalized patients. This marker has been demonstrated as potentially able to reduce antimicrobial exposure without harm among infected patients, even though there is a shortage of solid evidence to support its use. The scarcity of head-to-head comparisons between CRP and PCT to guide antibiotic therapy highlights the preference for PCT in developed countries in spite of its limited availability. Well-designed multicenter studies testing CRP-guided protocols of antibiotic therapy in hospitalized patients are highly desirable.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing Interests

The authors declare that they have no competing interests.

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Authors Contribution

R.F.D. and V.N. designed and conceived the review. R.F.D., U.G.H. and V.N. performed the literature searches. R.F.D., U.G.H., U.G.H. and A.C.R.B.P. drafted the manuscript. R.F.D. projected and designed the figure. V.N. coordinated the study. All authors contributed to the interpretation of the results and critically reviewed the manuscript.

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