

THE ROLE OF BIOMARKERS IN DISTINGUISHING INFECTIOUS FROM NON-INFECTIOUS DISEASES

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Abstract

Background. The use of C-reactive protein (CRP) and procalcitonin (PCT) as guiding biomarkers in treating severe infections could improve the use of antibiotics. Biomarker dynamics are more reliable than single values in predicting sepsis when making the diagnosis and evaluating the response to antibiotic therapy. Both CRP and PCT used protocols have to be consistent with the clinical context and patient populations.

Objectives: reviewing the use of PCT and CRP in various clinical contexts and the patient population

Sources. We analyzed the most recent studies of these biomarkers for antimicrobial stewardship, including meta-analyses and original trials.

Content. According to several studies, critically ill patients who get antibiotic treatment under the guidance of CRP and PCT see a decrease in antibiotic exposure and related adverse effects. When patients are hospitalized in intensive care units (ICUs), CRP and PCT can be used to distinguish between viral and non-infectious causes of systemic inflammation. In septic patients, CRP levels are reliable to show a high negative predictive value (NPV), especially on day 1 of ICU admission. Consequently, CRP levels decrease during therapy with appropriate antibiotics in the next 3 days.

Implication. In addition to other clinical and laboratory parameters, CRP and PCT provide information about the risk of the bacterial infection worsening or improving under appropriate treatment. These improve antibiotic treatment decisions, allowing individualized treatment regimens with reduced overall antibiotic exposure.

Keywords: CRP, PCT, biomarkers, sepsis, systemic inflammation.

Rezumat

Introducere. Utilizarea proteinei C-reactive (CRP) și a procalcitoninei (PCT) ca biomarkeri în tratamentul infecțiilor severe ar putea îmbunătăți utilizarea antibioticelor. Dinamica biomarkerilor este mai fiabilă decât determinările unice în prezicerea sepsisului atunci când se pune diagnosticul și se evaluează răspunsul la terapia cu antibiotice. Atât în cazul CRP, cât și PCT, protocoalele utilizate trebuie să fie în concordanță cu contextul clinic și cu populațiile de pacienți.



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Objective. *Ne-am propus revizuirea utilizării PCT și CRP în diverse contexte clinice și populații de pacienți*

Surse. *Am analizat cele mai recente studii ale acestor biomarkeri pentru ghidarea terapiei antimicrobiene, inclusiv meta-analize și studii originale.*

Conținut. *Potrivit mai multor studii, în cazul pacienților în stare critică care primesc tratament cu antibiotice ținând cont de valorile CRP și PCT se înregistrează o scădere a expunerii la antibiotice și a efectelor adverse asociate. Atunci când pacienții sunt internați în unități de terapie intensivă, CRP și PCT pot fi utilizate pentru a distinge între cauzele virale și neinfecțioase ale inflamației sistemice. La pacienții septici, nivelurile CRP sunt de încredere în ceea ce privește valoarea predictivă negativă (NPV) ridicată, în special în ziua 1 de internare la UTI. În consecință, nivelurile CRP scad în timpul terapiei cu antibioticele adecvate în următoarele 3 zile.*

Implicații. *Pe lângă alți parametri clinici și de laborator, CRP și PCT oferă informații despre riscul de agravare sau ameliorare a infecției bacteriene sub tratament adecvat. Acestea îmbunătățesc deciziile de tratament cu antibiotice, permițând regimuri individualizate de tratament, cu expunere globală redusă la antibiotice.*

Cuvinte cheie: *CRP, PCT, biomarkeri, sepsis, inflamație sistemică.*

Introduction

Systemic inflammation can indicate infection, but it can also stem from non-infectious sources such as vasculitis, cardiac ischemia, pulmonary embolism, bowel perforation, or pancreatitis. In cases of systemic infection, effective treatment involves supportive care and the timely administration of antimicrobial agents, with early intervention being crucial in managing sepsis⁽¹⁾.

Current guidelines suggest initiating empiric antibiotic therapy even before the specific infectious agent is identified. Treatment protocols and knowledge of the local microbiota serve as the starting point for this strategy⁽¹⁾. Nevertheless, confirming the presence of infection typically requires time, and inaccuracies in antibiotic prescriptions can substantially increase mortality rates. Additionally, excessive use of antibiotics contributes to the development of bacterial resistance. Consequently, it is extremely

crucial to have a reliable method to differentiate g caused by infection from various other underlying causes.

Two biomarkers, CRP and PCT, have undergone extensive research in diagnosing inflammatory responses related to infections. However, both have their advantages and limitations when it comes to predicting the infectious origin.

Methods

This study reviews PCT and CRP usage in various therapeutic contexts and patient populations, focusing on studies and meta-analyses published between 2005 and 2022.

C-reactive protein (CRP)

CRP was the first acute-phase protein to be found, and it got its name from its capacity to precipitate *Streptococcus pneumoniae*'s C-polysaccharide. A key component of the nonspecific acute-phase response is CRP, a very sensitive marker for tissue injury, infection, and systemic inflammation. Hepatocytes are the primary organs responsible for its synthesis, and interleukin (IL)-6 specifically stimulates this production⁽²⁾.

In a calcium-dependent way, this protein binds to parts of damaged cell membranes and polysaccharides from bacteria and fungus. When the body undergoes an acute-phase stimulus, the concentrations of CRP in the bloodstream increase swiftly, from 10-100-fold every 6-72 hours, up to 1.000-fold^(3,4). Peak levels frequently appear 48 hours following the stimulation (Table 1). In healthy adults, the typical CRP concentration is below 0.1 mg/dL, but during inflammation, it can surge to over 50 mg/dL. After the triggering event subsides, CRP levels drop exponentially

in the next 20h. However, in sepsis patients CRP levels might stay persistently high for a longer period. CRP levels may also increase due to a broad spectrum of diseases, including burns, pericarditis, pancreatitis, intestinal inflammation, rheumatologic illness, solid cancers, and hematologic malignancy⁽³⁾.

In ICU patients, CRP has been thoroughly investigated as a predictor for an infection caused by bacteria. Patients with infections have been reported to have it at higher levels compared to individuals with non-infectious systemic inflammatory conditions. The optimal range for diagnosing infection falls between 5-10 mg/dL⁽⁴⁾. Infections caused by viruses and fungi often have lower CRP values than infections caused by systemic bacteria. During viral infections, interferon- α can inhibit hepatocytes' CRP production. However, it might be difficult to differentiate between bacterial and nonbacterial diseases by looking at CRP levels since individuals who have both types of infections frequently have similar CRP values. In almost 90% of patients, significantly elevated CRP values (>35 mg/dL) have been associated with infection⁽⁵⁾.

CRP in pneumonia

Diagnosing community-acquired pneumonia (CAP) poses consistent challenges, particularly because initial chest X-rays might not reveal infiltrates within the first 24-72 hours of the infection.

To confirm the presence or absence of pneumonia, CT scans were performed on individuals who had been clinically diagnosed with CAP. The study revealed that a significantly elevated CRP level proved to be a reliable predictor of CAP in patients with a chest X-ray showing false-negative results. Conversely, a low CRP level was valuable in ruling out CAP in patients with a chest X-ray showing false-positive results⁽⁶⁾. A recent



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study suggested that in adult people with infections of the respiratory tract, CRP cut-offs for initiating therapy and interrupting antibiotics should be less than 2 mg/dl and more than 10 mg/dl, respectively. However, other studies did not support these recommendations. (Table 2)^(7,8).

However, compared to the general hospital population, CRP may be more useful in differentiating between bacterial and nonbacterial illness among people with severe illness. (Table 2). The mean CRP levels were significantly lower among the H1N1 group (11.8 mg/dL) than in the people with bacterial pneumonia group (36.3 mg/dL) in a study that includes 16 H1N1 ICU patients as well as 9 ICU patients who had bacterial pneumonia. According to this study, individuals with bacterial pneumonia could be recognized with 100% sensitivity and 87.5% specificity if their CRP level was higher than 20 mg/dL.

However, there is not much established about CRP's function in fungal infections. Immunocompromised individuals in a single research had higher CRP values during invasive fungal infection (11.2-26.9 mg/dL), nevertheless less than in bacteremia patients (16.0-38.7 mg/dL)⁽⁵⁾. A different research that focused on fungal infections and involved high-risk postoperative patients discovered that a CRP threshold of >10 mg/dL was useful in differentiating between bacterial and

fungal infections, with a sensitivity of 82% and a specificity of 53%. Increased CRP levels frequently suggest bacterial infection origins instead of fungal origin. However, further research is necessary to establish appropriate cutoff values and precisely determine sensitivity and specificity. CRP's effectiveness as an infection marker increases when used in conjunction with other biomarkers. BioVAP, a multicenter study, explored the kinetics of biomarkers to predict Ventilator-Associated Pneumonia (VAP) and revealed that both CRP levels and the rate at which CRP changes over time serve as reliable indicators for the occurrence of VAP (Table 2)⁽⁹⁾.

A "probability of infection score" was created in a separate research, which included fever, tachycardia, increased white blood cell count, tachypnea, and an increased Sequential Organ Failure Assessment score (SOFA) in addition to a CRP level >6.0 mg/dL. The sensitivity and specificity of this scoring method in identifying infections in intensive care unit patients were around 90%⁽⁵⁾.

CRP in sepsis

There is insufficient evidence to support the validity of an isolated CRP determination in patients suspected of sepsis, as two meta-analyses with sensitivity and specificity ranges of 78%-80% and 60%-61%, respectively⁽¹⁰⁾. The use of various cut-off

	CRP	PCT
Properties	Acute phase protein	Hormone precursor
Normal values	<0.5mg/dl	<0.5 ng/ml
Maximum peak	> 1000 x NV	> 10 000 x NV
Source	Hepatocytes	All cells and macrophages
Time to increase after insult	4-6h	3-4h
Time to peak concentration	36-50h	24h
Half-time	19h	22-35h
Interactions		
Steroids	No effect	FN
Immunosuppression	No effect	FN
Neutropenia	No effect	FN
Renal failure	No effect	FP
Renal replacement therapy	No effect	FN
Chronic liver failure	FN	No effect
Bacterial vs viral infection	Poor	Controversial

Table 1. The biology of CRP and PCT

NV – normal value; FN – false negative; FP – false positive

	Indications	Limitations
PCT	- To withhold initial antibiotic treatment, when combined with clinical assessment in CAP - To guide antimicrobial stewardship in sepsis - To shorten the antibiotic duration	- PCT initial value depends on the time spent between the diseases' onset and the admission. - False positive value in renal failure, dialysis, immune-suppression, autoimmune diseases, cystic fibrosis, pancreatitis, trauma, pregnancy, malaria, high volume transfusion - In sepsis Delta values are necessary
CRP	- To detect inflammatory status, to potentially use anti-inflammatory treatment in CAP - To detect cut-off of potentially usefulness of antibiotic therapy - Delta CRP increases are useful to predict poor evolution of VAP	- CRP initial value depends on the time spent between the diseases' onset and the admission. - False positive results in inflammatory, non-infectious diseases - False negative results in previous corticosteroid treatment or chronic hepatic diseases

Table 2. The benefits and limits of CRP and PCT

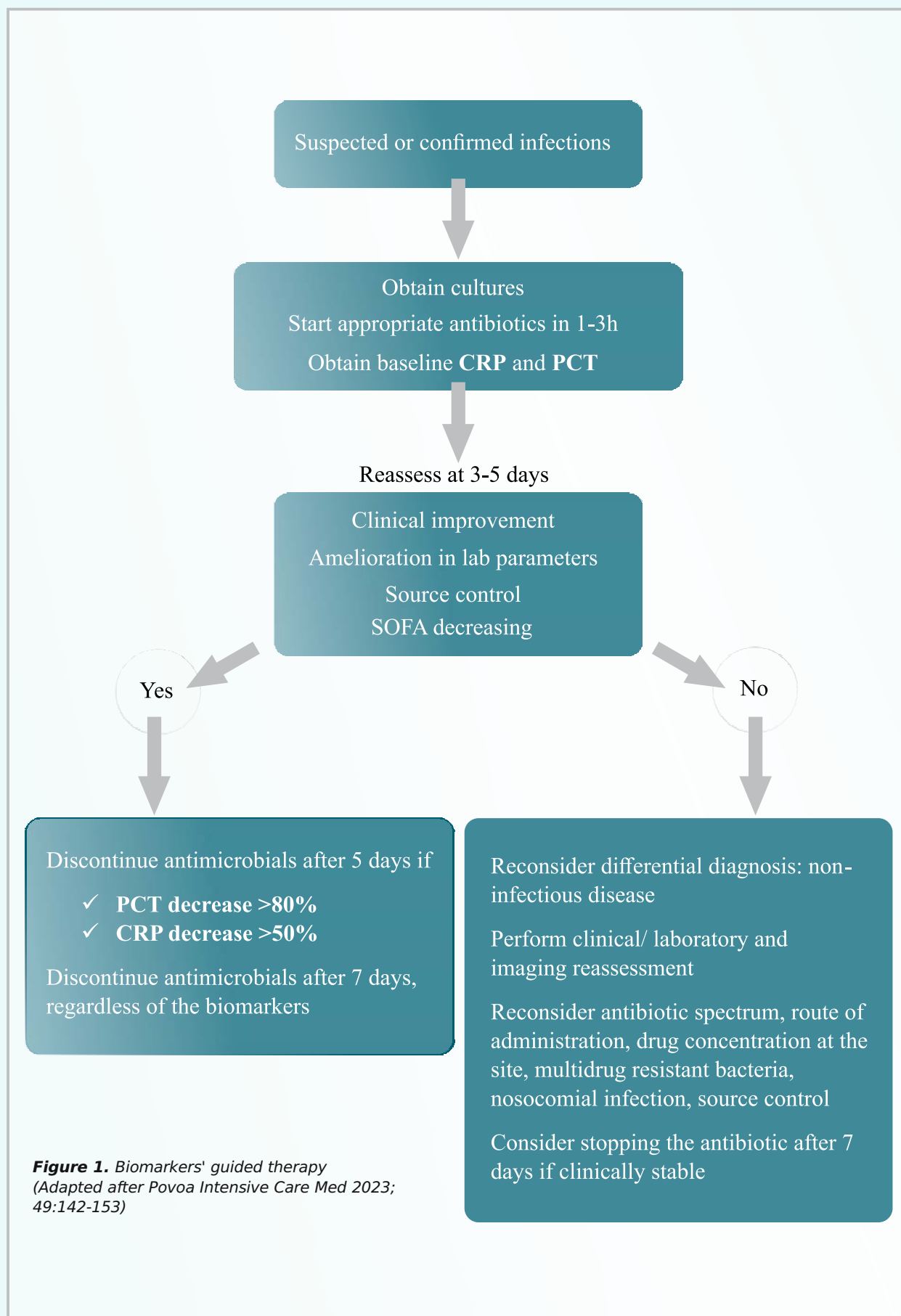


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	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Studies
PCT (ng/ml)	0.5	68.2	66.4	20.9	94.1	<i>Oksuz et al., 2015 (14)</i>
	0.5	76	69	17-28	95-98	<i>Hoeboer et al., 2015 (33)</i>
	0.9	71.9	69.1	24.5	94.6	<i>Hattori et al., 2014 (12)</i>
	0.5	74.2	70.1	26.1	95.1	<i>Kim et al., 2011 (31)</i>
	2	26.4	88.6	64	61	<i>Ljungstorm et al., 2017 (13)</i>
	2	56.8	94.1	98.7	21.1	<i>Demirdal et al., 2018 (32)</i>
CRP (mg/dl)	2	85.1	14.5	44.1	61.4	<i>Ljungstorm et al., 2017 (13)</i>
	4.4	63	81	30	94	<i>Isaacman et al., 2002 (15)</i>
	5	93.2	9.5	11.8	91.4	<i>Oksuz et al., 2015 (14)</i>
	5	90	68	81	83	<i>Li et al., 2014 (16)</i>
	12.5	66.1	50.4	17.6	90.3	<i>Hattori et al., 2014 (12)</i>

Table 3. The predictive values of CRP and PCT





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points - typically encompassing 2 mg/dL to 50 mg/dL - also affects the inconsistent validity of CRP in clinical research (Table 3). Most of them emphasize the high NPV of CRP, especially on day 1 of ICU admission⁽¹¹⁻¹⁵⁾. In a prospective multicenter cohort study designed to assess 53 biomarkers for distinguishing sepsis from non-septic systemic inflammatory response syndrome (SIRS), the findings demonstrated poor discriminatory ability. None of the combinations of biomarkers performed better than CRP alone in this regard⁽¹⁹⁾. A recent paper noted that the positive predictive value (PPV) for CRP is 0.56 (95% CI [0.53-0.59]) with the best cutoff of 13 mg/dl⁽²⁰⁾. Interestingly, a significantly lower threshold of 6.28 mg/dl was linked to a statistically significant increase in mortality⁽²¹⁾.

CRP-guided therapy

In critically sick patients, CRP can be an invaluable tool to evaluate antibiotic treatment (Scheme I). In contrast to patients who required a change in medication, individuals who responded effectively to antibiotics reported a quick decrease in their CRP levels after Day 1 according to a prospective observational trial including 50 ICU patients with illnesses they had either acquired in the hospital or the community. CRP levels greater than 2.2 mg/dl during the

initial 48 hours of treatment were linked to improper antibiotic use, with a 77% sensitivity and a 67% specificity⁽⁸⁾.

In individuals diagnosed with severe CAP, the administration of suitable antibiotic therapy led to a reduction of over 60% in CRP levels by Day 3 and exceeding 90% by Day 7 of treatment. Consequently, significant decreases in CRP levels are typically observed by Day 3 or 4 of appropriate antibiotic therapy. It is important to note, however, that this effect might be more prominent in non-intensive care patients compared to those in intensive care settings. Several studies have investigated biomarker-guided strategies to guide antibiotic duration when shorter, fixed durations of therapy are considered.

By using the duration of antibiotics guided by CRP, they established that in individuals who had uncomplicated Gram-negative bacteria infections, 7-day set intervals of antimicrobial therapy were not inferior to 14-day intervals of antibacterial treatment in terms of 30-day clinical failure rates⁽¹⁹⁾. Furthermore, a greater number of patients quit using antimicrobial medication by the fifth follow-up day, and the time-to-event analysis revealed a significantly decreased level of antibiotic exposure. It is possible to conclude that CRP may cause the intervention group's average antibiotic therapy duration to be shortened by one day⁽²⁰⁾.

Procalcitonin (PCT)

Calcitonin is a peptide that regulates calcium, and PCT is a 116 amino acid precursor. Thyroid C cells naturally release procalcitonin, which is subsequently broken down into calcitonin.

Serum PCT levels are nearly undetectable (<0.05 ng/ml) in healthy persons. However, during infections, gene expression of PCT is upregulated in various tissues such as liver or lung neuroendocrine cells, adipocytes, and even macrophages. Because these tissues are unable to decompose PCT into calcitonin, the levels of PCT in the serum increase fast. Pro-inflammatory cytokines including IL-6 and IL-1 as well as bacterial lipopolysaccharides, or endotoxin, cause PCT expression in tissues other than the thyroid gland.

In contrast, interferon- γ , a mediator of viral infections, inhibits PCT expression. It is worth noting that PCT is not entirely specific to bacterial infections. Non-infectious causes such as neuroendocrine malignancies such as small-cell lung cancer, thyroid gland C-cell carcinoma, and gastrointestinal tract-neuroendocrine tumors can also induce elevated PCT levels (Table 1). In addition, acute conditions leading to elevated PCT levels include trauma, pancreatitis, rhabdomyolysis, and cardiac arrest⁽²²⁾. PCT levels also typically rise after surgery, particularly in individuals experiencing abdominal surgery⁽²¹⁾.

In bacterial infections, PCT levels rise rapidly within 2-4 hours, with a half-life of 22-26 hours. The peak level typically occurs 24-48 hours after symptom onset⁽²²⁾. PCT levels drop significantly, reaching a 50% reduction by day 4 of ICU admission and nearly normalizing by day 7, even in septic patients. It is important to note that in individuals with significant renal impairment, PCT clearance is impaired by 30%-50%. (Table 2)⁽²³⁾.

PCT demonstrates significant diagnostic accuracy for distinguishing viral from bacterial infections. A meta-analysis of three research reported that PCT, with a cut-off range of 0.5-5 ng/ml, has a 92% sensitivity and 73% specificity for differentiating between bacterial and viral infections. Moreover, PCT is valuable in discerning invasive bacteria from fungal infections. In a study with immunocompromised individuals, 21 patients (interquartile range: 0.1-0.5 ng/ml) with bacteremia had substantially higher PCT levels than 13 patients (fungemia). In order to detect fungemia in this cohort, the researchers found that a low PCT level of less than 0.5 ng/ml and a moderately increased CRP level of less than 30 mg/ml were 85% specific and 81% sensitive, respectively. Consequently, a non-bacterial disease would be more likely to be suggested by increased levels of CRP and a reduced PCT level⁽⁵⁾.

PCT in pneumonia

In patients with severe CAP, PCT has been studied to identify bacterial coinfection in influenza cases. Some studies have suggested that in individuals diagnosed with influenza, PCT levels might possess a higher NPV for ruling out bacterial coinfection. Indeed, a recent meta-analysis concluded that procalcitonin lacks sensitivity in CAP and is not highly accurate in distinguishing between viral and bacterial infections^(24,25).

According to current international guidelines, PCT is not recommended for diagnosing Ventilator-Associated Pneumonia (VAP)⁽²⁶⁾. Instead, these guidelines propose that PCT may be valuable in guiding the duration of antibiotic treatment in specific scenarios, such as cases involving inappropriate antibiotic therapy, infections caused by multidrug-resistant (MDR) microorganisms, or scenarios



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where second-line antibiotics like colistin and tigecycline are necessary. Other studies found that serial PCT measurements and stopping antibiotics when the PCT level fell more than 80% from baseline or below 0.25 ng/ml decreased the risk of adverse drug events and improved survival⁽²⁷⁾.

The average duration of the antibiotherapy was reduced from 10.4 days to 7.5 days in a meta-analysis including over 3000 pneumonia patients and this reduction was accompanied by a lower incidence of failure of therapy and mortality⁽²⁸⁾. These positive effects on mortality associated with PCT-guided antibiotic management could be related to different reasons, such as side effects decrease in antibiotics and a reduced risk of secondary *Clostridioides difficile* infection⁽²⁹⁾.

PCT in sepsis

Several authors have explored the PPV of PCT in patients with severe infections, but the results indicated poor diagnostic accuracy and minimal influence on the decision to initiate antimicrobial therapy⁽³⁰⁾. With few exceptions, the NPV of PCT appears to be more reliable (Table 3)^(11-13, 31-33). Indeed, it is crucial to emphasize that there is no universally agreed-upon Procalcitonin PCT cut-off value for diagnosing sepsis. Various studies have either reported no specific cut-off value while others utilized a range between 0.5 and 2 ng/ml⁽³⁴⁾. PCT levels correlate with mortality when the

value rises above 7 ng/ml⁽³⁵⁾. Even though the PCT value could be useful for reducing antibiotic duration in selected cases, PCT as a single test is not reliable for predicting sepsis in ICU patients and should not be used to start antimicrobials.

PCT-guided therapy

Once sepsis is suspected, the physician should assess the patient's clinical course 48-72 hours later⁽³⁶⁾. Any delay in clinical and biological improvement due to ongoing septic complications, inadequate antibiotic therapy, or misdiagnosed disease is important to note (Figure 1).

In patients with VAP, procalcitonin measurements taken at baseline and on day 4 of treatment have shown the ability to predict survival and differentiate between patients with favorable and poor outcomes. Persistent high PCT levels on day 4 of antibiotic therapy indicated a failure to control infection⁽³⁶⁾.

In the field of clinical practice, if patients continue to show high levels of biomarkers even after 3 or 4 days of antibiotic treatment, it should raise concerns about the effectiveness of the therapy. This situation calls for a thorough diagnostic and therapeutic approach. However, it is important to show caution when solely relying on biomarkers to make decisions about diagnosis or treatment adjustments.

A multicenter experiment called PRORATA investigated how procalcitonin influenced ICU patients' intake of antibiotics. Patients in the PCT cohort had specific thresholds for starting and stopping antibiotics based on their PCT levels. When infectious symptoms appeared, antibiotics were recommended only for patients with procalcitonin (PCT) levels exceeding 0.5 ng/ml.

Following antibiotic initiation, treatment discontinuation was contemplated if PCT levels fell below 0.25 ng/ml or if they were less than 0.5 ng/ml and decreased by at least 80% from the peak level. Patients in the procalcitonin group experienced significantly more antibiotic-free days, with a notable difference of 2.7 days, compared to those in the control group. This increase did not result in higher mortality rates or longer ICU stays⁽³⁷⁾. The latest sepsis guidelines encourage discontinuation of treatment rather than initiation of antibiotics according to the PCT value⁽¹⁾. Therefore, PCT-guided antibiotic prescribing holds the potential to reduce unnecessary antibiotic use, but it might be necessary to conduct daily PCT testing to ensure its effectiveness.

Results and discussion

CRP and PCT are valuable for distinguishing between infectious and non-infectious causes of systemic inflammation in ICU patients. Furthermore, increased CRP levels seem to serve as a reliable indicator of Community-Acquired Pneumonia in patients with a negative chest X-ray and suggest a bacterial infection. In septic patients, CRP levels exhibit a high Negative Predictive Value, especially on the first day of ICU admission. Utilizing CRP measurements can potentially reduce the duration of antibiotic therapy by one day in specific circumstances.

After initiating proper antibiotic therapy, the CRP and PCT levels typically decrease from 1 to 3 days. If there is no decrease in CRP or PCT levels during this period, the treatment is suggested to be ineffective. While PCT is not recommended for initiating antibiotic therapy, it can be valuable in guiding treatment decisions, potentially reducing the duration of antibiotic use by nearly three days without apparent adverse outcomes. Biomarkers should never be utilized as stand-alone tests; instead, it is imperative to perform evaluations in sequence rather than depending exclusively on a single value.

Conclusions

Together with other non-specific biological parameters, biomarkers of inflammation may be useful complementary tools for better evaluation of diagnosis and antibiotic treatment. At the patient's bedside, we should always be aware of the importance of constant clinical and biological evaluation, throughout the hospitalization period. In addition, it is important to understand how to correctly use inflammatory or sepsis biomarkers in clinical practice, taking into account the advantages and limitations of these tests.

ABBREVIATIONS

CAP – community-acquired pneumonia

CRP – C-reactive protein

ICU – intensive care units

IL – interleukin

NPV – negative predictive value

PCT – procalcitonin

POD3 – postoperative Day 3

PPV – positive predictive value

SIRS – systemic inflammatory response syndrome

SOFA – Organ Failure Assessment Score

VAP – ventilator-associated pneumonia



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AUTHORS' CONTRIBUTION

AC – confirm the authenticity of the synthesis; critically revised the article for important intellectual content

ADT – designed the paper; gathered the literature relevant material

AR – gathered the literature relevant material

IMC – gathered the literature relevant material;

MAR – gathered the literature relevant material

MCV – gathered the literature relevant material

VG – confirm the authenticity of the synthesis; critically revised the article for important intellectual content

VM – conceived and designed the paper; confirmed the authenticity of the synthesis

All authors read and approved the final manuscript.

CONFLICT OF INTEREST

There are no conflicts of interest, according to the authors.

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