PROCALCITONIN AND SEPSIS IN CRITICALLY ILL PATIENTS

Introduction

Sepsis is defined by the The Third International Consensus Definitions for Sepsis and Septic Shockas as potentially life-threatening organ dysfunction caused by a dysregulated host response to infection.

Nowadays, sepsis represents a global health problem, accounting for approximately 2% of all hospitalisations in developed countries, 6-30% of patients in intensive care units, and a mortality rate ranging from 28% to 56%. The incidence of sepsis has been increasing, which is attributed to a combination of multiple factors, such as the advanced age of patients, the growing number and complexity of diagnostic and therapeutic procedures, increased use of immunosuppressive drugs, and the rising number of infections caused by multidrug-resistant bacteria.

One-hour-diagnostic delay, attributable to lack of recognition during patient admission, is associated with a 7% reduction in survival.

The SOFA (Sequential Organ Failure Assessment) scale, and especially the qSOFA (Quick Sequential Organ Failure Assessment) and NEWS2 scales (which do not include laboratory parameters in their calculation), allow for the identification of organ dysfunction using simple clinical criteria, such as alterations in respiratory rate, systolic blood pressure, and level of consciousness. These scales are used to quantify the severity of organ dysfunction, correlating with 10% increase in mortality for each additional point. Sepsis can evolve into septic shock, which is characterised by persistent hypotension, the need for vasopressors, and elevated lactate levels (>2 mmol/L), with a mortality rate of up to 40%.

The dysregulation of the immune response in sepsis results in:

1. Cytokine storm: Massive release of inflammatory mediators (IL-6, TNF-α) that perpetuate the systemic inflammatory response.
2. Microvascular alterations: Reduced tissue perfusion and ischemic damage.
3. Metabolic failures: Hypoxia and anaerobic metabolism, reflected in elevated lactate levels, which contribute to multi-organ dysfunction with high risk of mortality.

Sepsis-related organ dysfunction can lead to non-specific analytical alterations that should be monitored through the following analytical parameters:

- Blood glucose: Both hypoglycemia, due to increased metabolic rate, and stress hyperglycemia may occur.
- Ions, including calcium: Hypocalcemia (ionized calcium <1,1 mmol/L or <4,8 mg/dL) may affect myocardial function and vascular tone.
- Renal function, total bilirubin, and ALT liver enzymes: Alterations in these parameters can suggest renal or hepatic involvement.
- Coagulation studies: Increased prothrombin time (PT) and activated partial thromboplastin time (aPTT) suggest disseminated intravascular coagulation (DIC). A decrease in fibrinogen and an increase in D-dimer levels support the presence of consumption coagulopathy and DIC. These parameters are also included in the Phoenix Sepsis Score.
- Complete blood count: Leukocytosis, a normal leukocyte count, or leukopenia, with the latter being associated with worse prognosis. Thrombocytopenia (included in the pediatric SOFA score) and neutropenia are also linked to poorer prognosis.
- Arterial or venous blood gas: The most common finding is metabolic acidosis, secondary to tissue hypoperfusion.
- Serum lactate: An initial lactate level >2 mmol/L suggests hypoperfusion and is considered a criterion for shock in adult patients. Various studies show that lactate levels >3,5-4 mmol/L are associated with higher mortality and progression to organ dysfunction. A value >5 mmol/L is considered one of the criteria for septic shock according to the Phoenix Sepsis Score.

The need for early diagnosis has led to the search for a specific biomarker, which also allows for risk stratification and prognosis, and whose variation can monitor subsequent evaluation. Procalcitonin (PCT) has revolutionised sepsis management, enabling more precise diagnosis and more efficient antibiotic management. This approach, combined with clinical strategies and the role of the laboratory, has significantly improved the care of critically ill patients.

In addition to biomarkers, it is important to mention the gold standard technique for microbiological diagnosis of sepsis: blood cultures. These are essential for isolating the causative microorganism and studying antibiotic sensitivity. Ideally, they should be obtained before starting antibiotic treatment, as long as it does not significantly delay its initiation.

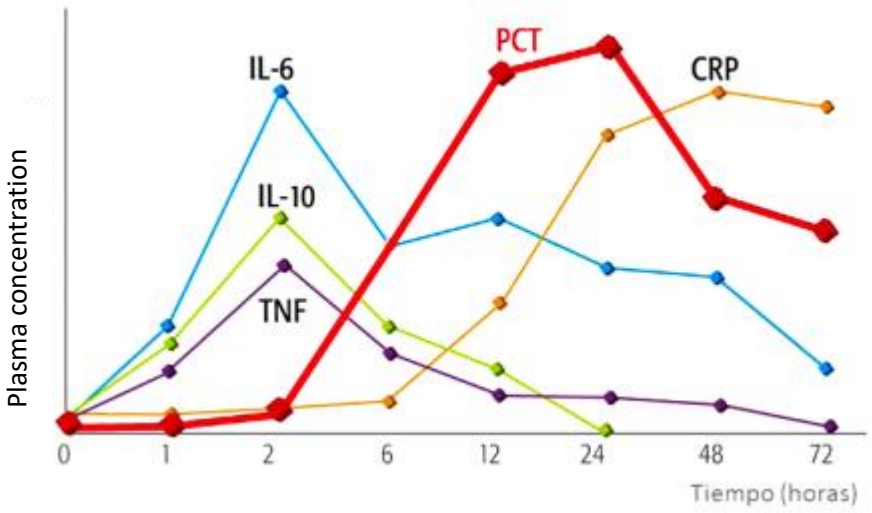
Other clinical samples (urine, sterile fluids, respiratory secretions, etc.) may also be cultured depending on the likely source of infection.

Main Biomarkers in Sepsis

Biomarkers are essential tools in the diagnosis and management of sepsis. They provide additional information beyond the clinical examination, enabling early detection of

bacterial infections, quantifying the severity and risk of infection, and monitoring disease progression and treatment response.

The following graph depicts the kinetics of various biomarkers related to sepsis and infection.



Time (hours)

As shown in the graph, cytokines such as IL-6, IL-10, and TNF have a very early release kinetic, starting to rise just one hour after the onset of the process. However, these biomarkers are eliminated quickly, becoming undetectable shortly after. Furthermore, they are not easily measurable and are expensive. Although they are initial indicators of systemic inflammatory response, when elevated due to an infection, they are not specific to bacterial etiology with systemic involvement, as they can also rise in viral infections or localised bacterial infections.

C-reactive protein and procalcitonin have proven useful biomarkers for identifying the risk of invasive bacterial infections.

C-reactive protein (CRP)

CRP is the classic biomarker used. It is an acute-phase reactant protein synthesized by the liver in response to any type of inflammation or tissue damage, including viral infections, localised bacterial infections, trauma, neoplasms, burns, tissue infarctions, etc. Although IL-6 is the primary stimulus for CRP synthesis, other cytokines such as IL-8 and IL-10 also contribute.

Due to its low specificity, CRP's utility in early infection diagnosis is limited by its kinetics, as it starts to rise at 12 hours, peaking at 48 hours, after other biomarkers like procalcitonin (PCT). Furthermore, the liver continues synthesizing CRP for several days, even after the inflammatory stimulus has disappeared, meaning its concentration may remain elevated even when the infection is resolving, which limits its prognostic value and use for guiding antibiotic therapy. Despite the aforementioned limitations, PCR is a parameter included in nearly all test catalogs of emergency laboratories in our country, and its measurement remains in the recommendations of certain societies, likely pending review based on new knowledge regarding biological markers of infection.

Procalcitonin (PCT)

PCT is the precursor polypeptide of calcitonin (CT), a hormone involved in calcium homeostasis, synthesised from the CALC-I gene located on chromosome 11. Under normal conditions, the transcription of the gene and formation of messenger RNA (mRNA) occurs selectively in certain cells, such as C cells in the thyroid and some neuroendocrine cells in the lungs. From this mRNA, preprocalcitonin, consisting of 141 amino acids, is synthesised, which is then processed into PCT, a 116-amino acid peptide. PCT has an aminoterminal region (N-PCT), a central calcitonin region (CT), and a carboxyterminal region (CCP-I). Through the action of prohormone convertase, PCT is fragmented into NPCT and the CT-CCP-I conjugate, which is then converted into immature CT through proteolysis. Following an amidation process in the C granules of thyroid cells, it becomes mature CT, along with free CCP-I. Since the conversion of PCT into CT occurs before secretion into the bloodstream, and because only weak extrathyroidal transcription of the CALC-I gene occurs in the absence of infection, PCT concentrations in healthy individuals are very low, with values less than 0.05 ng/mL being considered normal.

In situations of systemic inflammation, there is a generalised activation of the CALC-I gene expression, causing the entire body to behave like an endocrine gland. Under normal conditions, calcitonin mRNA is only detected in the thyroid and lungs, but during sepsis, it can be found in tissues and organs as diverse as the spleen, liver, testes, fat, or brain. The increase in the concentrations of CT precursors in the blood during infection occurs almost exclusively at the expense of extrathyroidal cells, with bacterial endotoxins and pro-inflammatory cytokines acting as stimuli. However, there is little increase in mature CT in the blood, since outside the neuroendocrine system, cells lack the necessary granules and enzymes for its processing. Additionally, the very signals secreted during bacterial infection, which act as stimuli for PCT synthesis, inhibit its conversion to CT. In contrast, during viral infection, PCT concentrations remain low due to the action of interferon-gamma (IFN-γ), a cytokine released during the infection.

Regarding kinetics, PCT induction is rapid, detectable within 3-6 hours after bacterial stimuli, peaking at 12-24 hours with a half-life of 24-36 hours. In the absence of stimulus, levels normalise in 72 hours, while persistently elevated PCT suggests poor prognosis. A 4-day non-decrease of 80% of initial PCT levels is associated with almost double the mortality rate compared to a reduction of 80%.

The specific pathway for PCT elimination has not been established, although it is likely degraded through proteolysis. According to studies conducted by Meisner et al., renal excretion of PCT is minimal, accounting for approximately one-third of the plasma concentration. Nevertheless, renal insufficiency may reduce the clearance of PCT, prolonging its half-life and thus affecting blood concentration.

It cannot be stated that PCT is the ideal biomarker for infection, as increases in its concentration can also be observed in non-infectious conditions.

False positives:

- In neonates, elevated concentrations are found physiologically during the first 48 hours of life, a period that some authors extend up to 60 hours, with even higher concentrations in premature infants.
- Critical situations, such as polytrauma, severe burns, pancreatitis, major surgery, prolonged cardiogenic shock, autoimmune diseases, neoplasms, etc.

False negatives:

- Localised infections
- Severe neutropenia

Despite this, PCT is currently the most useful biomarker in the diagnosis of infection and the prediction of bacteremia, the assessment of severity, decision-making regarding the initiation of antibiotic treatment, and a useful tool in its monitoring.

Indications and Interpretation of PCT Values

The measurement of PCT helps predict bacterial infection, distinguishing it from viral infections and other inflammatory processes, and differentiates between localised and systemic bacterial infections.

It is important to emphasise that procalcitonin should not be used in isolation, but rather in combination with clinical evaluation and other microbiological data to make therapeutic decisions.

It is highly useful in prognosis, including for elderly patients, oncology-hematology patients, and those with neutropenia. Thus, the measurement of a single PCT value provides an idea of the severity of the condition.

The interpretation of the obtained PCT values can be made as follows:

< 0,5 ng/mL: Healthy individuals, chronic inflammatory processes, viral infections, and localised bacterial infections. The presence of sepsis, severe sepsis, or septic shock is unlikely.

- 0,5-2 ng/mL: Viral infections and localised bacterial infections. The presence of septic shock is unlikely, but sepsis is possible. Serial measurements are recommended.
- 2-10 ng/mL: Systemic bacterial infection (sepsis) highly probable. Antibiotic treatment should be initiated.
- 10 ng/mL: Severe sepsis or septic shock highly probable, with a risk of developing multiple organ failure. Antibiotic treatment is required.

In a similar way, the following table (Table 1) refers to the main applications of PCT, as well as the values for its interpretation in each case.

Table 1: Summary of the interpretation of PCT values (ng/mL) obtained.

Healthy individuals: < 0,05
Possible bacterial infection: > 0,1
Probable bacterial infection: > 0,25
Possible sepsis (clinical severity): > 0,5
Probable bacteremia: > 1-2
Possible severe sepsis (SG) / septic shock (SS): > 5-10 ng/mL *SG: severe sepsis; SS: septic shock*
Patients with viral infection: < 0,5

Patients with localised bacterial infection: < 0,5
Chronic inflammation and autoimmune diseases: < 0,5

Antibiotic de-escalation based on procalcitonin levels is a recommended strategy in the management of sepsis and septic shock. According to the Surviving Sepsis Campaign guidelines, published by the Society of Critical Care Medicine, the American College of Chest Physicians and the Infectious Diseases Society of America, the use of procalcitonin can guide the duration of antimicrobial treatment in patients with sepsis.

The evidence from 14 randomised clinical trials (n = 4,499 patients) suggests that procalcitonin-guided management may improve mortality (RR, 0,89; 95% CI, 0,80 to 0.99) and reduce antibiotic exposure, although it does not affect the duration of ICU or hospital stay. However, the overall quality of the evidence is considered low due to variability in treatment algorithms, the frequency of procalcitonin monitoring, and the thresholds for antibiotic discontinuation.

To sum up, antibiotic de-escalation based on procalcitonin levels is a practice supported by the Surviving Sepsis Campaign, with potential benefits in reducing mortality and antibiotic exposure, although the evidence is of low quality, and further research is needed to standardise its use.

Indications and interpretation of procalcitonin in pediatric patients:

- Febrile syndrome of less than 24 hours of evolution (prioritise in children under 36 months of age with fever of unknown origin if indicated according to specific protocol).
- Suspected sepsis.
- Differential diagnosis of severe conditions: Acute pyelonephritis (APN)/cystitis, viral/bacterial meningitis, viral/bacterial pneumonia, septic arthritis/synovitis, etc.

Monitoring the evolution of an infectious process to assess early discontinuation of antibiotics.

Cut-off points:

- Fever of unknown origin <36 months, acute pyelonephritis (APN), febrile bronchiolitis, pneumonia, arthritis: >0,5 ng/mL
- Meningitis, sepsis: >1 ng/mL
- Sickle cell disease with fever of unknown origin: >2 ng/mL

In-hospital sepsis protocol:

The in-hospital protocol for sepsis prioritises early detection, immediate initiation of antibiotic therapy, and hemodynamic support for the patient.

Key elements of the sepsis code are based on identifying the clinical signs of sepsis/septic shock: respiratory rate, oxygen saturation, systolic blood pressure, heart rate, level of alertness or consciousness, and temperature.

Biomarkers such as procalcitonin, CRP, and lactate help reinforce the initial diagnosis. Early intervention, starting antibiotic treatment within the first 4-6 hours, is aimed at reducing mortality and the length of hospitalisation for patients with sepsis.

Conclusions:

Sepsis represents a clinical and analytical challenge that requires a multidisciplinary strategy.

The integration of procalcitonin as a key biomarker in the management of sepsis has significantly improved clinical outcomes. Its ability to differentiate bacterial infections, guide antibiotic therapy, and monitor patient progression makes it an indispensable tool in clinical practice. However, its use must be supported by comprehensive clinical evaluation, well-defined algorithms, and constant laboratory support to maximise its effectiveness in critically ill patients.

Paloma Salas Gómez-Pablos
Responsable Laboratori Urgències CST
CATLAB
Tel. 93.731.00.07 - ext. 7121 / 609016262
psalas@catlab.cat

Ana Pardo
Responsable Lab. Urgències Hospital Mútua de Terrassa
CATLAB
Tel. 93.736.50.50 - ext. 19403 / 608.36.70.36
apardo@catlab.cat

Diana Visiedo
Responsable Lab. Urgències Martorell
CATLAB
Tel. 93.774.20.20 - ext. 15000 / 630.994.729
dvisiedo@catlab.cat

Bibliography:

Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use. Clin Chem Lab Med. 2019 Aug 27;57(9):1308-1318

Philipp Schuetz. How to best use procalcitonin to diagnose infections and manage antibiotic treatment. Clin Chem Lab Med 2023; 61(5): 822–828

Kevin J. Downes, Julie C. Fitzgerald, Scott L. Weissb: Utility of Procalcitonin as a Biomarker for Sepsis in Children

Laura Molina, Julia García. Nuevos marcadores de sepsis. Código sepsis. Formación continuada AEFA 2022

Laura Evans, Andrew Rhodes Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Critical Care Medicine November 2021 • Volume 49 • Number 11

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021 Critical Care Medicine 49(11):p e1063-e1143, November 2021. | DOI: 10.1097/CCM.0000000000005337