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PROCALCITONIN

A Novel Biomarker for
Bacterial Infections and Sepsis




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INTRODUCTION

An ideal biomarker for bacterial infection should not only allow early diagnosis, but also inform about the course and prognosis of the disease and guide therapeutic management. Since the first report in 1993 on the association of serum procalcitonin (PCT) levels with bacterial infection¹ there is a solid body of evidence in the literature that this marker is being increasingly recognized as a good marker of bacterial infections and sepsis and therefore as an important tool in clinical practice.

The aim of this booklet is to provide an overview of the main indications of this parameter based on selected references. It intends to give an orientation on how PCT may provide added value to the clinical decision process.

PCT, however, will not be the 'magic bullet' and some of the limitations of this marker are also discussed. Clinicians should always interpret PCT values in the clinical context of the patient. The increase in PCT reflects the continuous development from a healthy condition to the most severe consequences of bacterial infection (severe sepsis and septic shock). Therefore, optimal cut-off values for PCT are variable and dependent on factors such as the clinical setting, the site and extent of the infection and the presence of co-morbidities.





SUMMARY

- 1** What is Procalcitonin?
- 2** Contribution of PCT in the Diagnosis and Monitoring of Sepsis
- 8** PCT Differentiates Effectively
- 10** Interpretation of Results
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WHAT IS PROCALCITONIN?

PCT is the prohormone of calcitonin (CT). Whereas CT is secreted by the C-cells of the thyroid after hormonal stimulation, PCT can be produced by numerous cell types and organs after proinflammatory stimulation, especially when caused by bacterial challenge.²

In healthy people, plasma PCT concentrations are found to be below 0.05 ng/ml, but can increase up to 1000 ng/ml in patients with severe sepsis or septic shock.

Elevated PCT levels may indicate bacterial infection accompanied by a systemic inflammatory reaction.

Localized infections do not generally cause circulating PCT increases. Slightly elevated PCT concentrations are observed in bacterial infections with minor systemic inflammatory response.

Very high values have been observed during acute disease conditions with severe systemic reactions to an infection, in cases of severe sepsis or septic shock.

Clinical need for earlier detection of sepsis

Early detection and specific clinical intervention has been shown to be crucial for the improved outcome of patients with sepsis. However, sepsis can be difficult to distinguish from other, non-infectious conditions in critically ill patients with clinical signs of acute inflammation and negative microbiological results. Therefore, in the early phase of the disease process it may be difficult to decide on the appropriate therapeutic measures for the individual patient.

Additional **specific information** may be helpful **to increase the accuracy of sepsis diagnosis at an early stage.** A parameter that fulfills these demands to a high degree is procalcitonin.



CONTRIBUTIONS OF PCT IN THE DIAGNOSIS OF SEPSIS



Definitions

Definitions for the terms of “SIRS”, “sepsis”, “severe sepsis” or “septic shock” have been proposed by the ACCP/SCCM consensus conference in 1992, and are now widely used (see below table 1).³

Table 1

SIRS and sepsis definition

(ACCP/SCCM-criteria)

SIRS (Systemic Inflammatory Response Syndrome)	2 or more of the following criteria: <ul style="list-style-type: none"> • Temperature > 38°C or < 36°C • Heart rate > 90 beats/min • Respiratory rate > 20 breaths/min or PaCO₂ < 32 mm Hg (<4.3 kPa) • WBC > 12 000 cells/μL or < 4 000 cells/μL or > 10% immature (band) forms
Sepsis	Documented infection together with 2 or more SIRS criteria
Severe Sepsis	Sepsis associated with organ dysfunction, including, but not limited to, lactic acidosis, oliguria, hypoxemia, coagulation disorders, or an acute alteration in mental status.
Septic Shock	Sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time when perfusion abnormalities are detected.

ACCP: American College of Chest Physicians

SCCM: Society of Critical Care Medicine

Fast and highly specific PCT increase in bacterial infection and sepsis

One major advantage of PCT compared to other parameters is its early and highly specific increase in response to severe systemic bacterial infections and sepsis.^{4,5} Therefore, in septic conditions, increased PCT levels can be observed 3-6 hours after an infectious challenge.

PCT levels are usually low in viral infections, chronic inflammatory disorders or autoimmune processes. PCT levels in sepsis are generally greater than 0.5-2 ng/mL and often reach values between 10 and 100 ng/mL, or considerably higher in individual cases, thereby enabling diagnostic differentiation between these various clinical conditions and a severe bacterial infection (sepsis) (Figure 1).

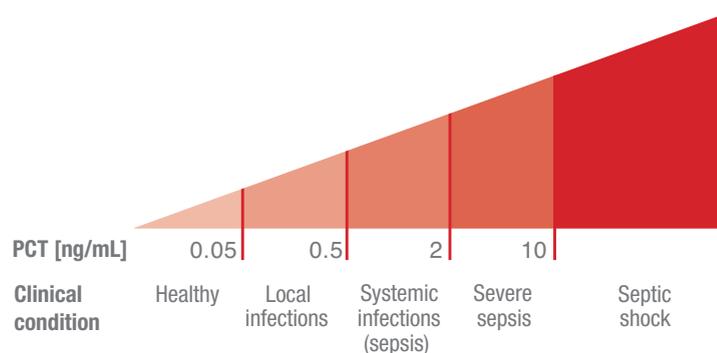


Figure 1

PCT increase reflects the continuous development from a healthy condition to the most severe states of disease (severe sepsis and septic shock).

PCT - useful parameter for early sepsis diagnosis

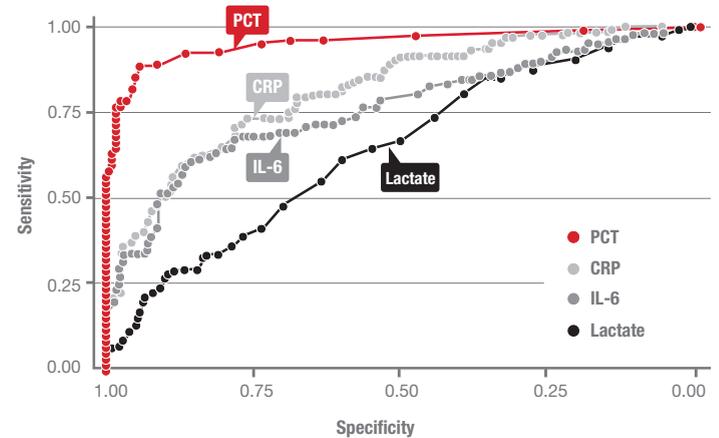
Among several laboratory parameters, PCT has been shown to be the most useful.^{4,5,6,7} PCT showed the best performance for differentiating patients with sepsis from those with a systemic inflammatory reaction not related to an infectious cause (Figure 2)

FIGURE 2

Increased Diagnostic and Prognostic Value:

Procalcitonin (PCT) is the only laboratory parameter shown to have made a significant contribution to the clinical diagnosis of sepsis.⁴

Compared to serum lactate, PCT has shown to be far more predictive for sepsis.⁵



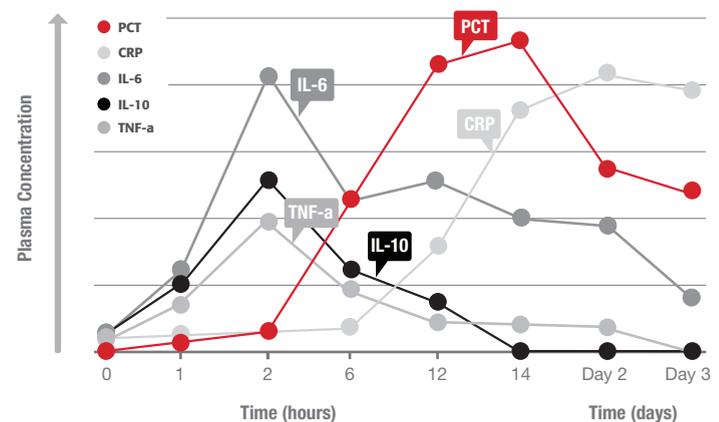
Rapid, specific response

PCT is distinguished from other markers by its early and highly specific increase in response to severe systemic bacterial infections and sepsis.^{4,5}

FIGURE 3

Increased PCT levels can be observed within just 3 – 6 hours after an infectious challenge.

24-hour half-life: PCT decline is consistent with an improving clinical condition.

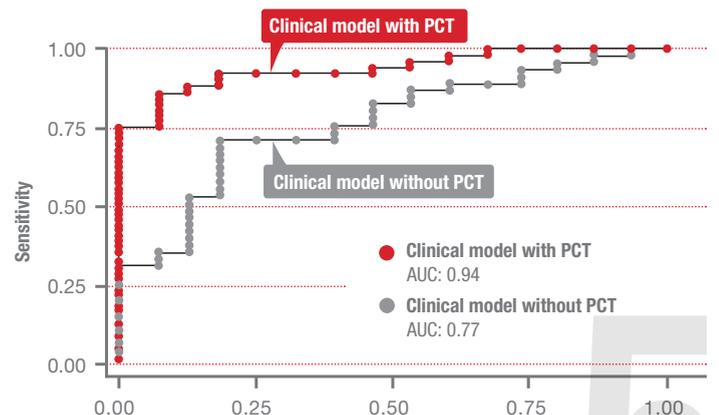


PCT improves accuracy of clinical sepsis diagnosis

Moreover, PCT was shown to be the **only** laboratory parameter that made a significant contribution to the clinical diagnosis of sepsis (Figure 3).⁴

FIGURE 4

Accuracy of sepsis diagnosis based on a clinical model with and without PCT.⁴

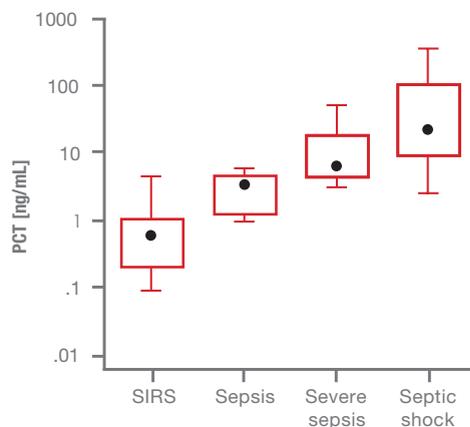


Increased PCT values - indicator for the severity of infection and organ failure

FIGURE 5A, B

Differentiation between SIRS*, sepsis, severe sepsis and septic shock by PCT and IL-6.⁴

* Systemic Inflammatory Response Syndrome



PCT development accurately reflects the progression of the disease with greater reliability than other parameters (Figure 5a-d).

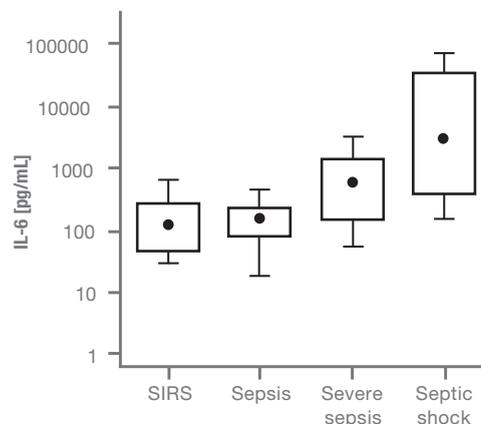
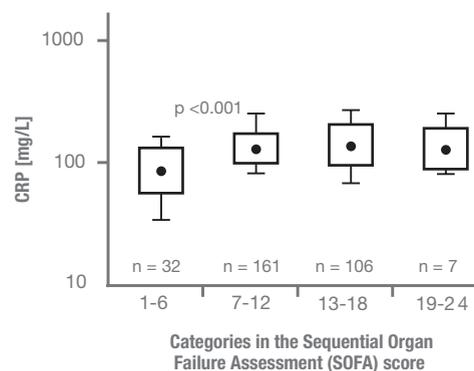
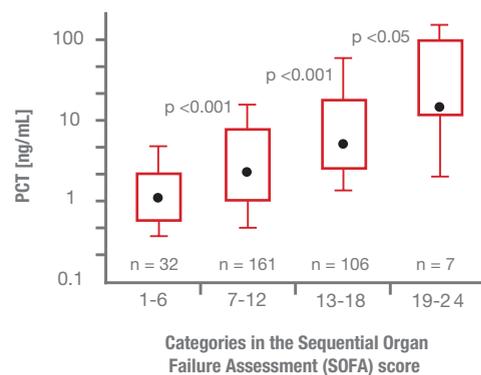


FIGURE 5C, D

Assessment of severity of disease (increasing organ dysfunction) by PCT and CRP.⁸



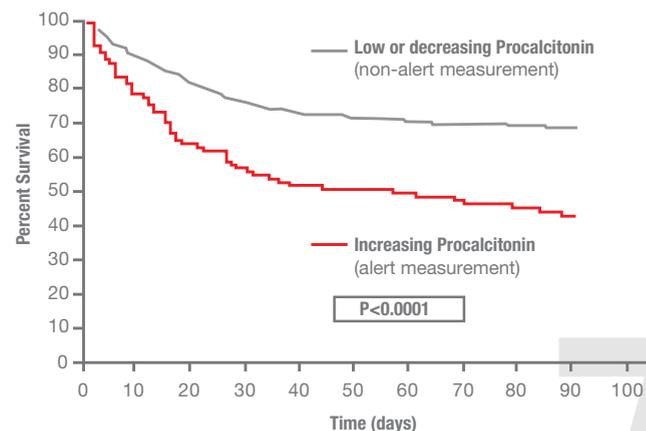
Increased PCT values - indicator of mortality risk for patients in ICU

A high maximum procalcitonin level and a procalcitonin increase for 1 day are early independent predictors of all-cause mortality in a 90 day follow-up period after intensive care unit admission.⁹ Mortality risk increases for every day that procalcitonin increases.

Levels or increases of CRP and white blood cell count do not seem to predict mortality.⁹

FIGURE 6

PCT increase and 90-day mortality in the ICU.



PCT DIFFERENTIATES EFFECTIVELY BETWEEN SEPSIS AND SIRS OF NON-INFECTIOUS ORIGIN

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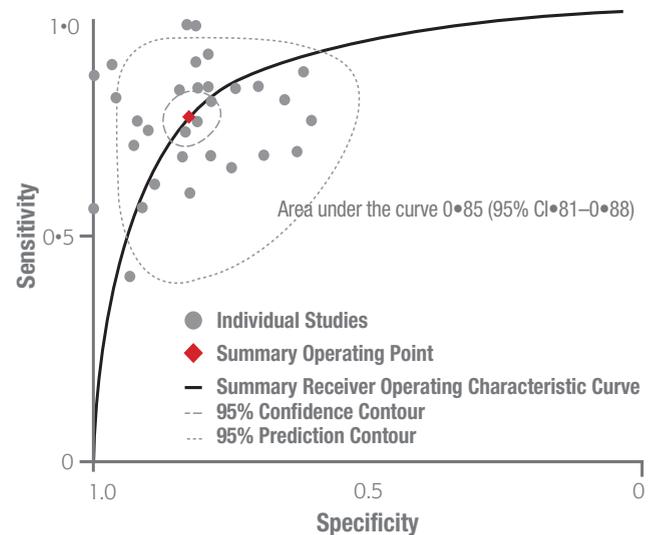
- 30 robust studies included for final meta analysis
- 3244 critically ill patients in analysis

PCT differentiates effectively between Sepsis and SIRS

Important information for critically ill patients for whom diagnostic decision making is of utmost importance.

PCT is a helpful biomarker for early diagnosis of Sepsis

Procalcitonin is one of the most promising parameters for early sepsis diagnosis. Results should be interpreted in context of the medical history, physician examination and microbiological assessment. However, a reliable test of infection is still absent.



Wacker, C, et.al., Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis, Published on-line www.lancet.com/infection, February 1.¹⁰

INTERPRETATION OF RESULTS



Healthy individuals: Determination of normal values with a highly sensitive assay revealed normal values to be below 0.05 ng/mL.¹¹

PCT serum concentrations are elevated in clinically relevant bacterial infections and continue to rise with the increasing severity of the disease. However, as an expression of individually different immune responses and different clinical situations, the same focus of infection may be associated with varying individual elevations in PCT concentrations. Therefore, clinicians should always use PCT results in conjunction with the patient's other laboratory findings and clinical signs, and interpret the concrete values in the context of the patient's clinical situation.*

The reference ranges below are provided for orientational purposes only.

Diagnosis of Systemic Bacterial Infection/Sepsis ^{2,3}

SIRS, sepsis, severe sepsis, and septic shock are categorized according to the criteria of the consensus conference of the American College of Chest Physicians/Society of Critical Care Medicine.³

PCT < 0.5 ng/mL

Systemic infection (sepsis) is not likely.

Local bacterial infection is possible.

Low risk for progression to severe systemic infection (severe sepsis).

Caution: PCT levels below 0.5 ng/mL do not exclude an infection, because localized infections (without systemic signs) may be associated with such low levels.

Also if PCT is measured very early after a bacterial challenge (usually < 6 hours), these values may still be low. In this case, PCT should be re-assessed 6-24 hours later.¹²

PCT ≥ 0.5 and < 2 ng/mL

Systemic infection (sepsis) is possible, but other conditions are known to induce PCT as well.*

Moderate risk for progression to severe systemic infection (severe sepsis). The patient should be closely monitored both clinically and by re-assessing PCT within 6-24 hours.

PCT ≥ 2 and < 10 ng/mL

Systemic infection (sepsis) is likely, unless other causes are known.*

High risk for progression to severe systemic infection (severe sepsis).

PCT ≥ 10 ng/mL

Important systemic inflammatory response, almost exclusively due to severe bacterial sepsis or septic shock.

High likelihood of severe sepsis or septic shock.

* See Limitations page 12

Limitations

Increased PCT levels may not always be related to systemic bacterial infection.

Several situations have been described where PCT can be elevated by non-bacterial causes. These include, but are not limited to:

- neonates < 48 hours of life (physiological elevation)¹³
- the first days after a major trauma, major surgical intervention, severe burns, treatment with OKT3 antibodies and other drugs stimulating the release of pro-inflammatory cytokines¹⁴

- patients with invasive fungal infections, acute attacks of plasmodium falciparum malaria¹⁴
- patients with prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, small cell lung cancer, medullary C-cell carcinoma of the thyroid.¹⁴

Low PCT levels do not automatically exclude the presence of bacterial infection.

Such low levels may be obtained, during the early course of infections, in localized infections and in subacute endocarditis. Therefore, follow-up and re-evaluation of PCT in clinical suspicion of infection is pivotal. The PCT measuring technique should be chosen according to clinical use.

PRACTICAL ASPECTS OF PCT TESTING

	Frequently Asked Questions	Answers
PCT induction and kinetics	Rapid increase after bacterial infection	PCT increases ~3 hours after bacterial infection, reaching maximum values after 6-12 hours. ^{2,14}
	Half-life time <i>in vivo</i>	About 24 hours
Sample material and stability	Sample material for PCT measurement	Human serum or plasma may be used. ^{14*} PCT values measured in patient samples of arterial blood are ~4% higher than in samples from venous blood. ¹³ Current assay formats are suitable for use with human serum or plasma only. Other human body fluids or samples from other species cannot be used.
	Stability <i>In vitro</i> stability	Very stable <i>in vitro</i> , no special requirements for pre-analytical sample handling and storage ¹⁴
	At room temperature	~2% decomposition rate during the first two hours after blood collection, ~10% decomposition during the first 24 hours
	At -20 °C	Stable for 6 months
	Freeze/thaw, 3 cycles	< 2% loss of PCT in the sample

* For patient monitoring, the same sample matrix should always be used.

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