Solutions for Emergency Diagnostics

VIDAS Emergency Panel

VIDAS B·R·A·H·M·S PCT

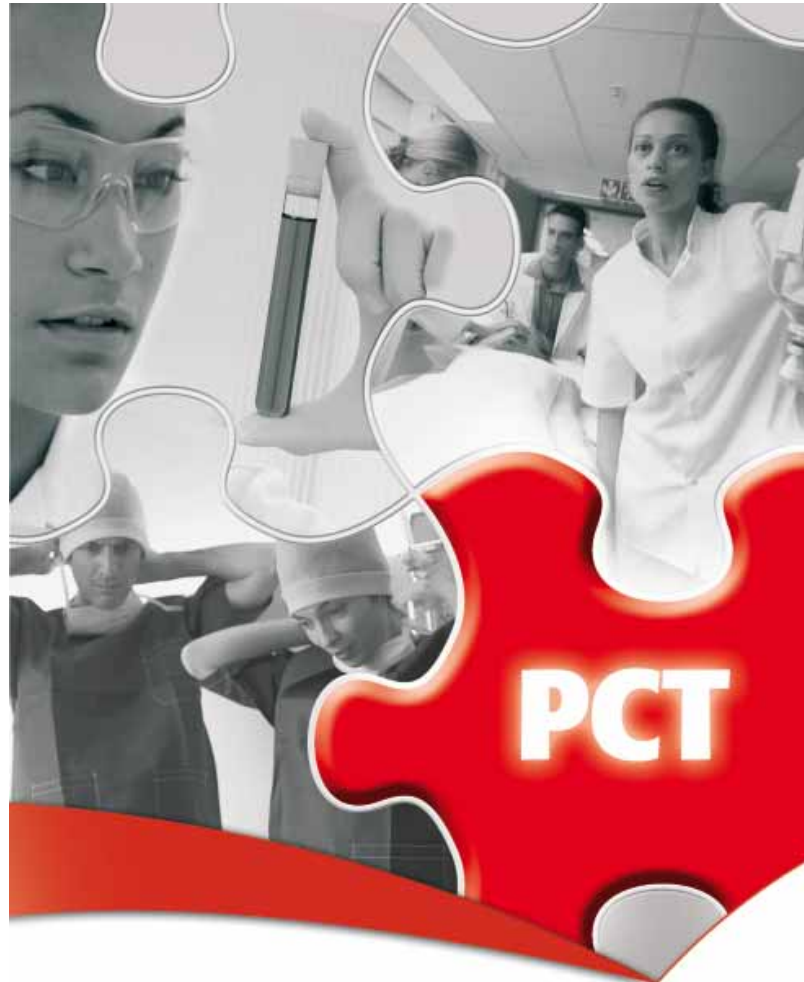| Bacterial Infection		
VIDAS B.R.A.H.M.S PCT	ref 30 450	60 tests
Venous Thromboembolism		
D-Dimer Exclusion ™	ref 30 442	60 tests
Cardiac		
Troponin I Ultra	ref 30 448	60 tests
Myoglobin	ref 30 446	30 tests
CK-MB	ref 30 421	30 tests
NT-proBNP	ref 30 449	60 tests
Digoxin	ref 30 603	60 tests

Your stamp

**The information in this booklet is given as a guideline only
and is not intended to be exhaustive.
It in no way binds bioMérieux S.A. to the diagnosis established
or the treatment prescribed by the physician.**

BIOMÉRIEUX

Procalcitonin
Bacterial Infections and Sepsis

from diagnosis,
the seeds of better health

BIOMÉRIEUX

Introduction

An ideal marker 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 infection [1] there is a solid body of evidence in the literature that this marker fulfils these demands to a high degree [2]. These studies show that PCT 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 is not strictly a practical guide but intends to give an orientation on how PCT may provide added value to the clinical decision process, i.e. assist in diagnosis, assess prognosis, assist in treatment selection and monitoring. A promising application is the use of PCT as a tool to guide antibiotic therapy (antibiotic stewardship).

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.

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 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.
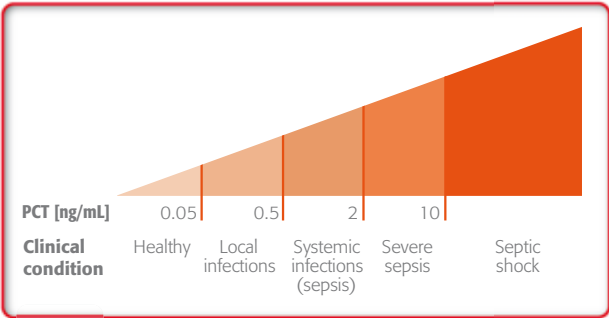
PCT [ng/mL]	0.05	0.5	2	10	
Clinical condition	Healthy	Local infections	Systemic infections (sepsis)	Severe sepsis	Septic shock

Figure 1   PCT increase reflects the continuous development from a healthy condition to the most severe states of disease (severe sepsis and septic shock).

Contents

Definitions

The sepsis syndrome is a complex continuum of clinical events with increasing severity and mortality. In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) published consensus definitions in order to create a universal language for diagnosing and treating sepsis.[3] These definitions were updated and extended in 2001.[4] The sepsis consensus definitions recognize the following progressive stages: "SIRS", "sepsis", "severe sepsis" and "septic shock" (see Table 1).

Table 1
**SIRS and sepsis definition
(ACCP/SCCM-criteria)**

SIRS (Systemic Inflammatory Response Syndrome)	2 or more of the following criteria: • Temperature > 38°C or < 36°C • Heart rate > 90 beats/min • Respiratory rate > 20 breaths/min or $PaCO_2$ < 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

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 which fulfils these demands to a high degree is procalcitonin.

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.**[5,6] 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).

PCT - useful parameter for early sepsis diagnosis

Among several laboratory parameters, PCT has been shown to be the most useful.[5,6,7,8] PCT showed the best performance for differentiating patients with sepsis from those with a systemic inflammatory reaction not related to an infectious cause (Figure 2a,b)

Figure 2:
Comparison of diagnostic performances of various markers for diagnosis of bacterial infection/sepsis

Figure 2a

PCT versus CRP[7]
PCT: Better differentiation of bacterial infection from non-infectious causes of inflammation.

Summary receiver operating characteristic (SROC) curves comparing serum procalcitonin (PCT; •) and C-reactive protein (CRP; •) markers for detection of bacterial infections versus non-infective causes of inflammation. Each point contributing to the SROC curve represents 1 study (total number of studies: 10; total number of patients: 905).
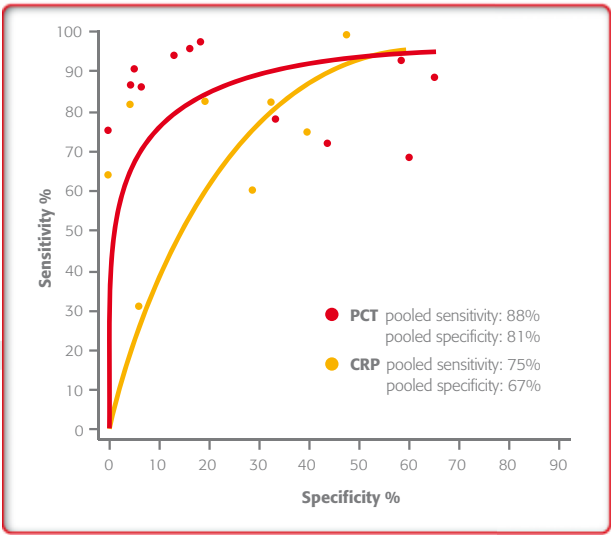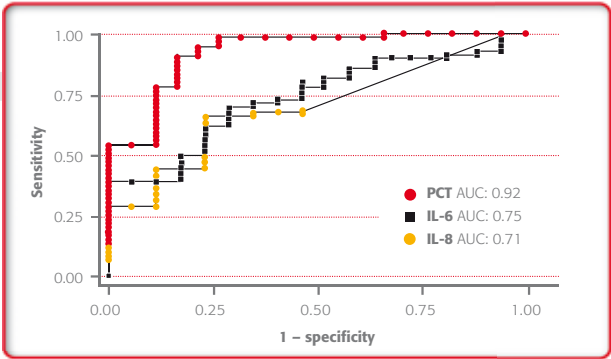

PCT pooled sensitivity: 88%
pooled specificity: 81%
CRP pooled sensitivity: 75%
pooled specificity: 67%

Figure 2b

PCT versus IL-6 and IL-8[5]
PCT: More accurate diagnosis of sepsis than IL-6 and IL-8.

Receiver operating characteristic (ROC) curves comparing serum procalcitonin (PCT), interleukin 6 (IL-6) and interleukin 8 (IL-8) for detection of sepsis on day of admission to ICU.
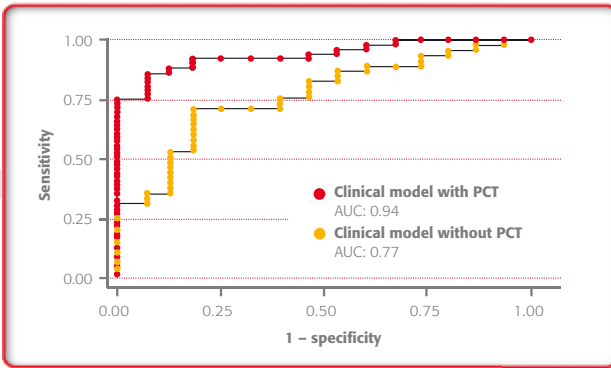

PCT AUC: 0.92
IL-6 AUC: 0.75
IL-8 AUC: 0.71

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).[5]

Information obtained from IL-6, IL-8 and CRP had no impact on the clinical diagnosis of sepsis on admission.

Figure 3

Accuracy of sepsis diagnosis based on a clinical model with and without PCT.[5]

Clinical model with PCT
AUC: 0.94
Clinical model without PCT
AUC: 0.77

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

PCT development accurately reflects the progression of the disease with greater reliability than other parameters (Figure 4a-d).

Differentiation between SIRS*, sepsis, severe sepsis and septic shock by PCT and IL-6.[5]

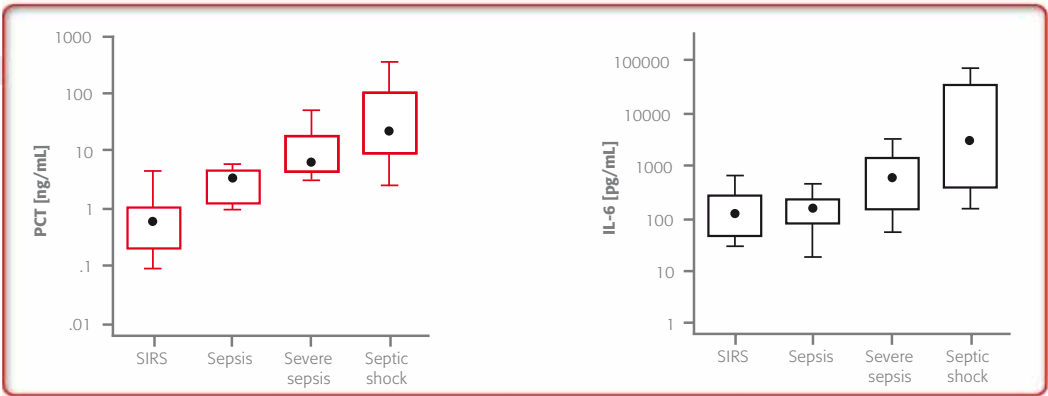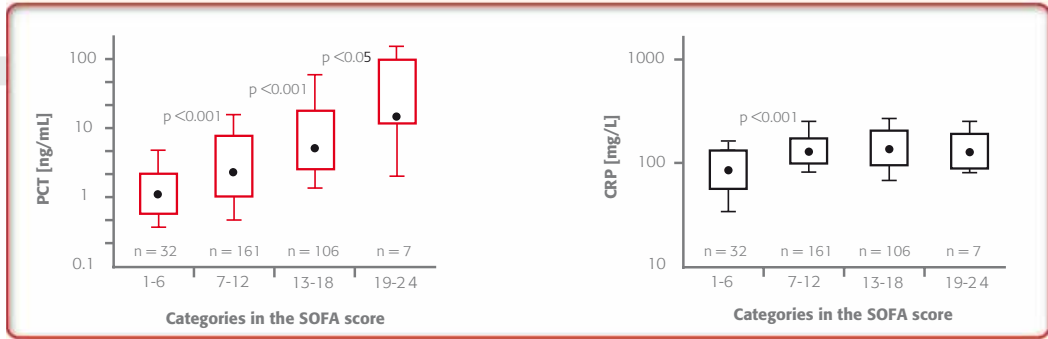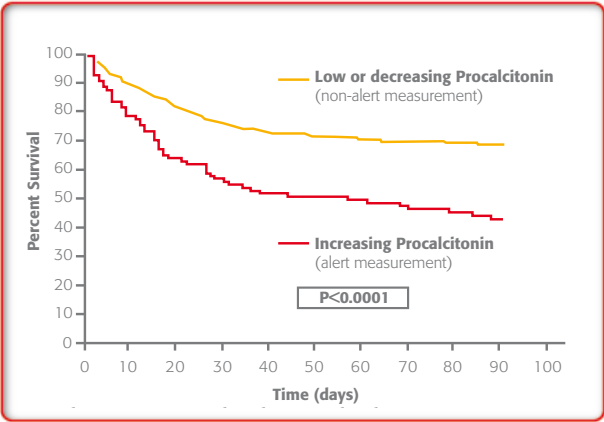* Systemic Inflammatory Response Syndrome

Assessment of severity of disease (increasing organ dysfunction) by PCT and CRP.[9]

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 independant predictors of all-cause mortality in a 90 day follow-up period after intensive care unit admission.[10] 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.[10]

PCT increase and 90-day mortality in the ICU.

PCT kinetics can be used to assess the effectiveness of treatment

As the septic infection resolves, PCT reliably returns to values below 0.5 ng/mL, with a half-life of 24 hours.[11] Consequently, *in vitro* determinations of PCT can be used to **monitor the course and prognosis of life-threatening systemic bacterial infections** and to tailor therapeutic interventions more efficiently.[12] This has been demonstrated for the monitoring of patients with ventilator-associated pneumonia (VAP).[13]
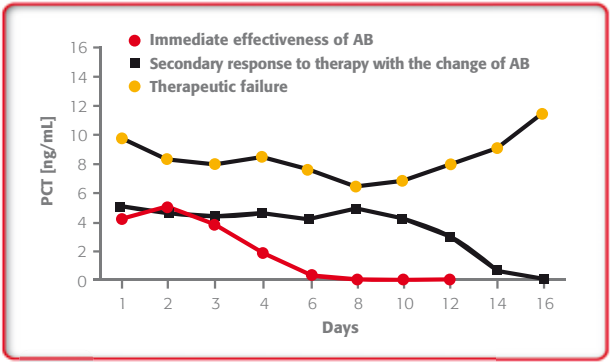

Typical course of PCT serum level according to patient's response to antibiotic treatment (n=109).[12]

Impact on therapeutic decisions and cost reduction

Initial studies on the economic implication of utilizing PCT in the diagnostic process have shown that **systematic use of PCT** for sepsis diagnosis and monitoring may also have a **positive impact on the reduction of antibiotic (AB) treatment,** therefore allowing a **shorter stay in the ICU and lower costs per case** (Figure 7).[14,15,16,17]
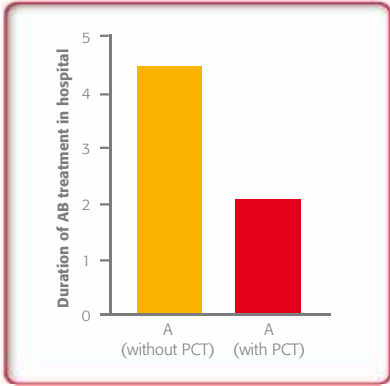
Cost savings by reduction of AB treatment days
PCT management of antibiotic use during an epidemic of enteroviral meningitis.
Unnecessary antibiotic treatment was stopped after exclusion of the bacterial infection. The decision to stop antibiotic treatment at a PCT value of < 0.5 ng/mL, without clinical counter-argument (inappropriately pretreated bacterial meningitis excluded), resulted in saving 2.4 days of antibiotics per patient (29,000 € in 2 months).[14]

LRTI – a major cause of sepsis

It is common knowledge that the majority of septic cases in the ICU are caused by LRTI.[18] LRTI should be considered as a potential pre-septic condition which requires early diagnosis and treatment. Such an approach may help to decrease the number of patients developing sepsis and, subsequently, increase their chance of survival.

Early clinical assessment of LRTI by sensitive PCT measurement

Sensitive PCT measurement techniques will capture **minor elevations of PCT in the blood circulation** [2,19,20] – therefore the **detection of clinically relevant bacterial infection is possible at a much earlier stage of the disease.**
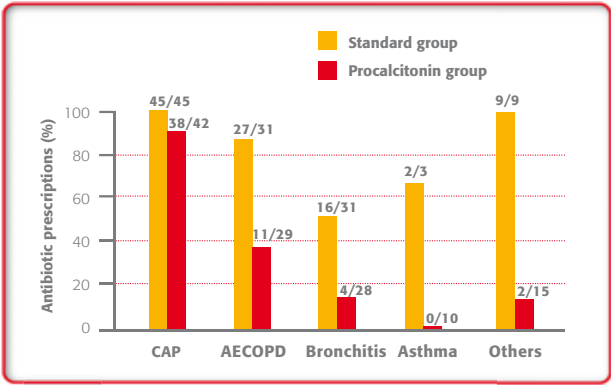
Figure 8a **AB treatment based on standard clinical assessment of LRTI (standard group n=119) and guided by PCT level (PCT group n=124)**[15] Patient groups with LRTI: CAP (Community-acquired pneumonia); AECOPD (Acute exacerbation of chronic obstructive pulmonary disease); Acute bronchitis; Acute exacerbation of asthma; Others.

Identification of LRTI patients who require antibiotic therapy

It has been clinically proven that due to the high specificity of PCT for bacterial infection, **PCT measurement at low concentrations can help to differentiate patients with clinically relevant LRTI who require antibiotic (AB) therapy** from those with viral infection or minor bacterial infection who do not require antibiotic treatment.[15]

Therefore, for patients who are clinically assessed as requiring treatment with antibiotics, but who have low PCT values (< 0.25 ng/mL), it is recommended that antibiotics should not be administered. For patients with very low PCT values (< 0.1 ng/mL), AB treatment is strongly discouraged (see decision algorithm, Figure 8b).

Using this PCT-based decision algorithm, patients with an infection of viral etiology or self-limiting disease are not unnecessarily exposed to antibiotics.
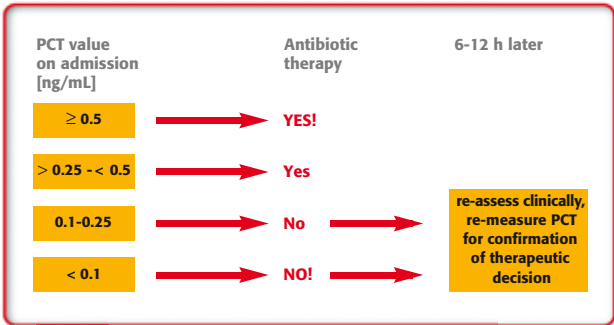
Figure 8b **PCT cut-offs for the guidance of AB therapy in patients with suspicion for bacterial LRTI**[15]

A comparison of the PCT-guided algorithm with standard clinical procedures has shown that AB prescription in LRTI cases could be reduced by nearly 50% without compromising clinical outcome.[15] The reduction in AB use based on PCT guidance was significant in all diagnostic sub-groups (Figure 8a). The usefulness of PCT-guided AB prescription was further confirmed in patients with acute exacerbations of COPD.[17] In AECOPD, AB prescription in the PCT-group was only 40%, compared with 72% in the standard group. This reduction was sustained for up to 6 months.[17]

Identification of CAP patients who require antibiotic therapy and guidance for AB duration

Approximately 20% of cases of community-acquired pneumonia (CAP) are viral in origin and do not require antibiotics. In bacterial CAP, the rapid initiation of antibiotic therapy is key for patient survival. A patient with bacterial CAP will usually be treated with AB for 10-14 days. However, there is considerable uncertainty on the optimal duration of AB therapy.

It has now been demonstrated that the initiation and duration of AB therapy can be guided by the measurement of PCT levels and its changes over the course of AB treatment.[16]
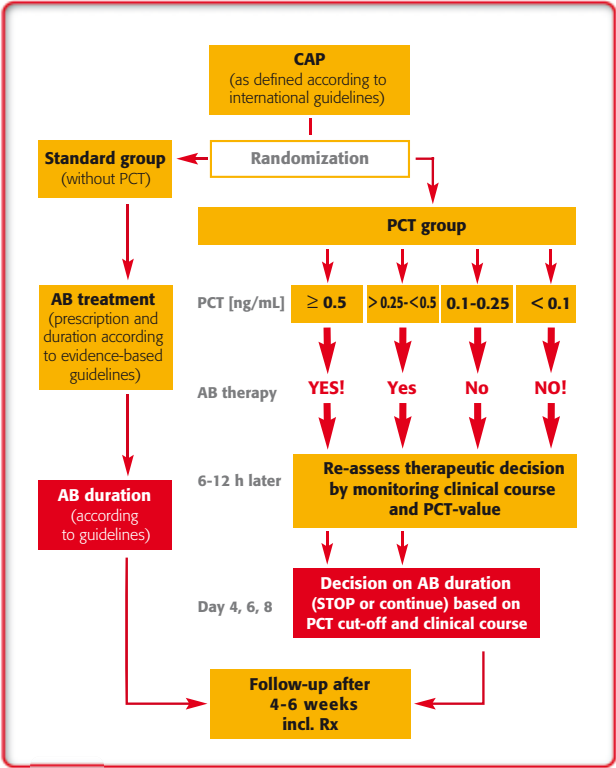
Figure 9a **PCT-based decision algorithm**
(design of interventional study)[16]

Therefore, having decided on a PCT-based AB guided therapy, PCT values will be closely monitored. **It is recommended to stop AB therapy when PCT falls to levels between 0.1 and 0.25 ng/mL.** When PCT levels fall below 0.1 ng/mL further continuation of AB therapy is strongly discouraged (Figure 9a).[16]
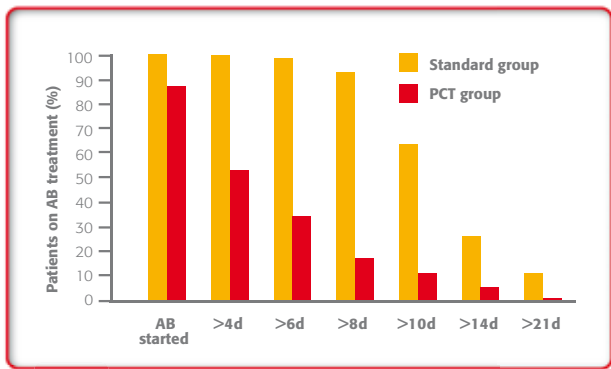
Figure 9b **AB use at days 0-21 with and without PCT guidance (PCT group n=151, standard group n=151)**[15]

The randomized study in CAP patients showed that PCT guidance shortened the duration of antibiotic therapy from a median of 12 to 5 days (Figure 9b), without affecting outcome.[16]

Also in septic ICU patients a randomized study indicated that PCT guidance resulted in a significant reduction in antibiotic duration without apparent harm.[21]

Medical and economic impact

Therefore, the integration of PCT into diagnostic and treatment algorithms allows both **earlier treatment** and also **more targeted use of clinical and financial resources by:**

• **reducing expenditure on antibiotics**
• **reducing the number of treatment days.**

This PCT-based decision algorithm allows the tailoring of the duration of therapy to the individual clinical situation **of each patient,** so that total AB use will be strictly limited according to specific clinical needs.

Interpretation of results

Healthy individuals: Determination of normal values with a highly sensitive assay revealed normal values to be below 0.05 ng/mL.[19]

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.[15]

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.

Differential diagnosis of Lower Respiratory Tract Infections [15,16,17]

PCT < 0.1 ng/mL	Indicates absence of bacterial infection. Use of antibiotics strongly discouraged, even in the presence of impaired pulmonary reserve in AECOPD.
PCT ≥ 0.1 and < 0.25 ng/mL	Bacterial infection unlikely. The use of antibiotics is discouraged.
PCT ≥ 0.25 and < 0.5 ng/mL	Bacterial infection is possible. Recommended to initiate antimicrobial therapy.
PCT ≥ 0.5 ng/mL	Suggests the presence of bacterial infection. Antibiotic treatment strongly recommended.

* See Limitations page 17

PCT reference ranges in neonates[22]

PCT values are physiologically increased during the first two days of life. Therefore, a different reference range applies to premature and newborn infants (Table 2).[22,23]

The reference range for the first two days of life changes within a few hours (Figure 10a). However, also during the first 48 hours of life, the PCT values of newborns suffering from early sepsis are significantly higher than those of healthy newborns (Figure 10b).

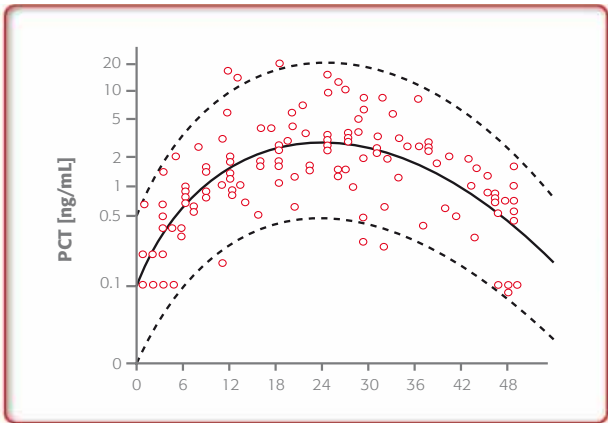The adult reference range applies from three days after birth.

Healthy newborns
95% reference range of PCT in healthy newborns (n=83) in the first 48 hours after birth. Individual measurements are illustrated. The unbroken line characterizes the geometric mean and the dotted lines the 95% reference range.[22]
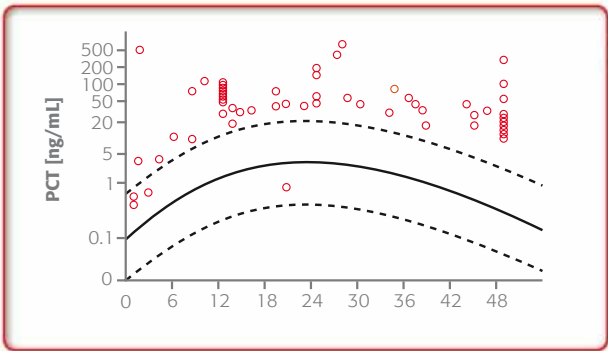

Septic newborns
PCT values in neonates presenting symptoms of sepsis within the first 48 hours of birth. Individual measurements are displayed. The unbroken line refers to the geometric mean while the dotted lines refer to the 95% reference range in the non-infected normal population.[22]

Age in hours	PCT [ng/mL]
0-6	2
6-12	8
12-18	15
18-30	21
30-36	15
36-42	8
42-48	2

Table 2: Normal range in neonates (covering 95% of all measurements)[22]

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)[22] (see reference values in Table 2 and Figure 10)
- 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 cytokines[24]
- patients with invasive fungal infections, acute attacks of plasmodium falciparum malaria[24]
- patients with prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, small cell lung cancer, medullary C-cell carcinoma of the thyroid.[24]

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 (see Figure 11).

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.[2,24]
	Half-life time *in vivo*		About 24 hours
Patient monitoring with PCT	Frequency of PCT measurement for patient monitoring		Minimum once per day
	Interpretation of PCT concentrations during **therapeutic monitoring***, *e.g.* after surgical removal of septic focus and/or after start of antibiotic therapy	‹	Large Reduction ~50% of PCT concentration per day over several days Indication for **success of therapeutic intervention** (surgery, antibiotic treatment)
		‹	Persistently high or continuously increasing PCT levels Indication for **non-controlled infectious process** justifying a re-assessment of therapeutic strategy [2,5,12,13,16,24]
	Interpretation of PCT concentrations during **infectious disease monitoring* of high-risk patients**, *e.g.* after extended surgery or polytrauma	‹	Low PCT levels or significant reduction of primarily increased PCT levels (*e.g.* after extended surgery) during the following days by ~50% per day to reach low values after a couple of days **No infectious complication**
		‹	Persistently increased PCT levels or newly increasing PCT levels **Infectious complication** [2,24,25]
Sample material and stability	**Sample material** for PCT measurement		**Human serum or plasma** may be used.[24] * PCT values measured in patient samples of arterial blood are ~4% higher than in samples from venous blood.[24]
			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 *In vitro* stability		Very stable *in vitro*, no special requirements for pre-analytical sample handling and storage [24]
	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.

Which cut-off to use?

bioMérieux provides a rapid quantitative PCT assay* for the compact automated immunoanalyzer VIDAS®.

PCT can be measured in either serum or plasma. Results are available in 20 minutes. **Choice of cut-off depends on intended clinical use (Figure 11).**
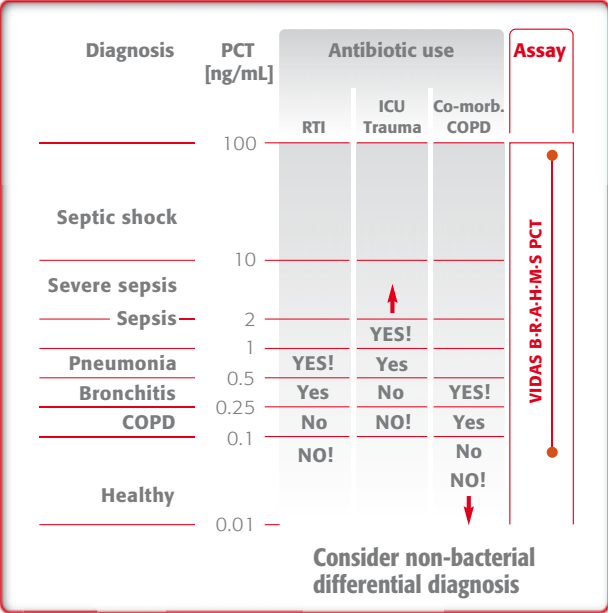
Figure 11 **Application of VIDAS BRAHMS PCT assay for various clinical settings** (adapted from Christ-Crain & Müller [2])

Cut-offs for clinical decision-making (e.g. decision on prescription and duration of AB therapy) **depend on the clinical setting.** E.g., for patients with COPD and suspicion of infection, antibiotics should be prescribed at a lower PCT value compared to a trauma patient without concomitant disease.

Decision to prescribe or withhold antibiotics should be re-assessed within the next 6-24 hours based on the patient's clinical picture and PCT level. These values should also be considered in the clinical decision-making process regarding the **duration of antibiotic therapy** as well as the clinical course of the disease.

* Reagent developed in collaboration with **BRAHMS** Aktiengesellschaft

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