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# Clinical Guide to Use of PROCALCITONIN for Diagnosis and PCT-Guided Antibiotic Therapy

PIONEERING DIAGNOSTICS

## The content of this booklet was kindly written by:

**Philipp Schuetz, MD, MPH**
Privat Dozent for Endocrinology and Internal Medicine
Medical University Department
University of Basel, Switzerland
Kantonsspital Aarau, Tellstrasse
CH -5001 Aarau, Switzerland

We wish to thank Dr. Schuetz for sharing his valuable knowledge on the practical use of procalcitonin in different clinical settings, and for his dedicated involvement in this booklet.



## Preface

In recent years, procalcitonin (PCT) has become an increasingly used blood biomarker for improved management of patients with systemic infections and sepsis.

Intended as a practical guide, this booklet provides clinicians with an overview of the potential usefulness and limitations of PCT for diagnosing bacterial infections, differentiating bacterial from non-bacterial diseases and other medical conditions, assessing disease severity and prognosis, and aiding clinical decisions on antibiotic therapy.

## Chapter 1

Discusses preclinical data on the regulation of PCT, the kinetics over time, and different diagnostic cut-offs according to clinical settings.

## Chapter 2

Examines the diagnostic and prognostic properties of PCT with examples from clinical research studies.

## Chapter 3

Illustrates the use of PCT for monitoring patients and for guiding antibiotic decisions for both initiation and duration of therapy in different types of infections and clinical settings.

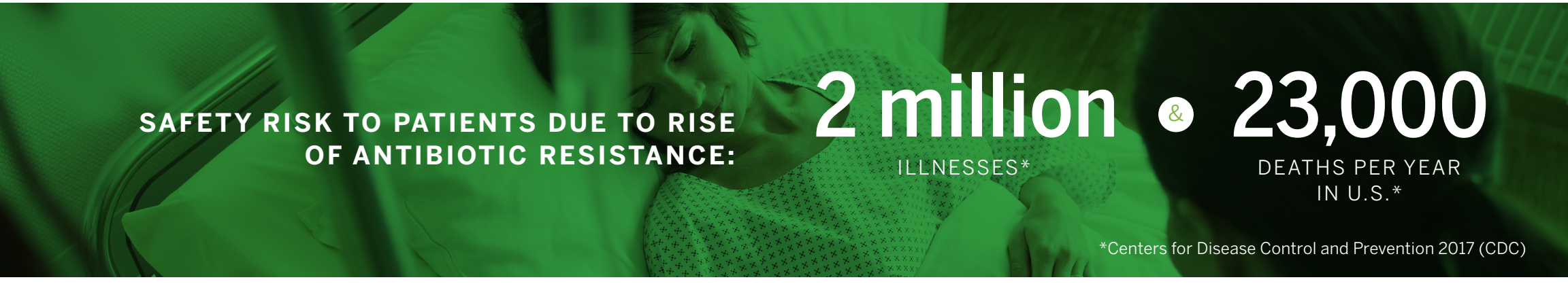
## Chapter 4

Explores some remaining issues that are important when using PCT.

**For easy reading and reference, look for the colored boxes highlighting the key points in each chapter.**

## Introduction

Antibiotic overuse and misuse represents a significant healthcare burden in terms of costs of treatment, but also in the increased risk of the resistant micro-organisms.




Emerging antimicrobial resistance and the serious issue of Clostridium *difficile* (C *diff*) infections calls for more effective efforts to reduce the unnecessary and prolonged use of antibiotics in self-limiting non-bacterial and resolving bacterial infections. To help achieve this aim, diagnostic tools and biomarkers are urgently needed to enable better assessment of a patient's risk of having an infection, and their response to antibiotic therapy.

One such blood biomarker is procalcitonin (PCT), which is increasingly used in clinical practice for improved patient management. Indeed, the FDA has recently approved new applications for PCT testing* to support the need for improved antibiotic stewardship, particularly for the management of patients with suspected lower respiratory tract infections (LRTI) and sepsis.

During bacterial infections, PCT blood levels rise within 4-6 hours. Its kinetics then mirror the severity of infection. PCT levels drop by about 50% daily when infection is controlled and responding adequately to antibiotics.[1]

* In February 2017, bioMérieux's VIDAS® B•R•A•H•M•S PCT™ became the first procalcitonin assay to be FDA-cleared as an aid for antibiotic stewardship in respiratory infections and sepsis.



Based on this regulation and kinetics, many studies have documented the clinical utility of PCT for different clinical settings and infections.

- PCT improves early detection of sepsis and risk assessment[2]
- PCT can aid in decision-making on antibiotic discontinuation for patients with suspected or confirmed sepsis[3]
- PCT used to monitor therapy for respiratory infections has led to a more tailored use of antibiotics with a reduction in antibiotic exposure of 30-70% depending on the clinical setting[4]
- PCT used to monitor therapy for respiratory infections has shown secondary gains such as lower risk of antibiotic-associated side effects, shorter length of hospital stays, and lower overall costs due to antibiotic savings[4]

Nevertheless, PCT is not a stand-alone test and does not replace clinical intuition or thorough clinical evaluations of patients. If used within well-defined clinical algorithms, PCT provides additional useful information and aids physicians in making rational clinical decisions in individual patient cases. As with any diagnostic test, knowledge of the strengths and limitations of PCT is a prerequisite for its safe and efficient use in clinical practice.[5]

# CONTENTS

# I – ABOUT PROCALCITONIN

## 1. What is procalcitonin and where is it produced?

Procalcitonin (PCT) is the precursor peptide – or prohormone – of the mature hormone calcitonin. PCT is released in multiple tissues in response to bacterial infections via a direct stimulation of cytokines,[6] and shows an interesting kinetic profile.[7]

**Cytokines** such as interleukin (IL)-6 and tumor necrosis factor (TNF) show a fast initial spike upon infection; however, levels return to normal within a few hours. The high variability of these markers has been a major challenge for their use in clinical practice.

**C-reactive protein (CRP),** on the other hand, increases slowly with a peak after 48-72 hours and a slow decrease thereafter. CRP is usually considered a biomarker for inflammation rather than infection.

In adults, PCT increases promptly within 4-6 hours upon stimulation and decreases daily by around 50% if the bacterial infection is controlled by the immune system supported by effective antibiotic therapy **(Figure 1). These characteristics make PCT an interesting biomarker for monitoring patients with systemic infections and sepsis and for more informed decisions on prescription and duration of antibiotic therapy.** As PCT levels do not show a steep decrease in non-responding infections, monitoring their course also has prognostic implications.

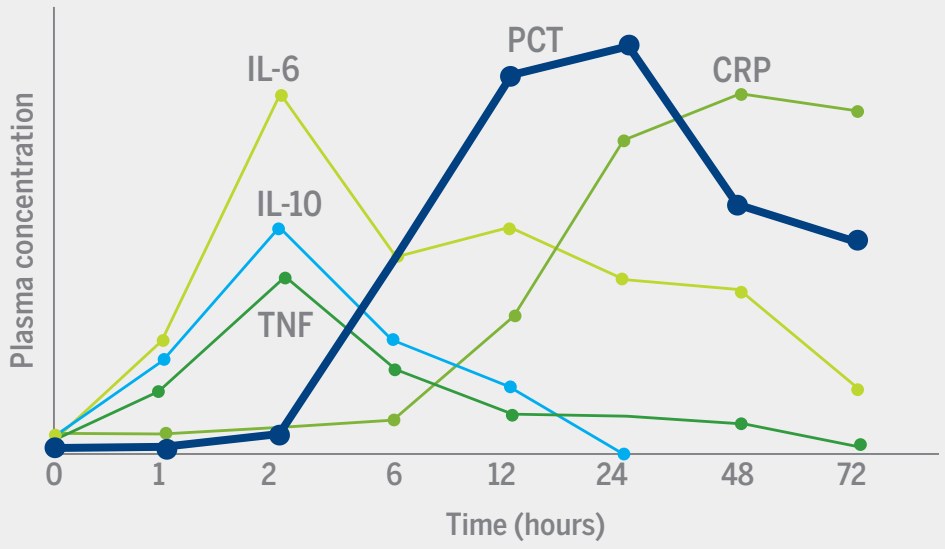



**Figure 1: Kinetic profiles of different biomarkers of bacterial infection.**

Pro-CT: Prohormone of calcitonin
CT-mRNA: Calcitonin-messenger ribonucleic acid
Adapted from Meisner M. *J Lab Med.* 1999;23:263–72.[1]

**Procalcitonin has an interesting kinetic profile, which enables monitoring of the individual patient's response to antimicrobial therapy.[7]**

## 2. How is procalcitonin regulated on a cellular level?

PCT production is induced in response to microbial toxins and to certain bacterial cytokines, particularly interleukin (IL)-1β, tumor-necrosis factor (TNF) and IL-6, and is released in the bloodstream where it can be measured **(Figure 2).**

Conversely, PCT production is attenuated by certain cytokines released in response to a viral infection, particularly interferon-γ (IFN-γ). This selective cellular mechanism makes PCT a useful diagnostic biomarker, which is **more specific for bacterial infections** compared to other inflammatory markers (i.e., C-reactive protein) and helps to **distinguish bacterial infections from other inflammatory reactions or non-bacterial infections.**

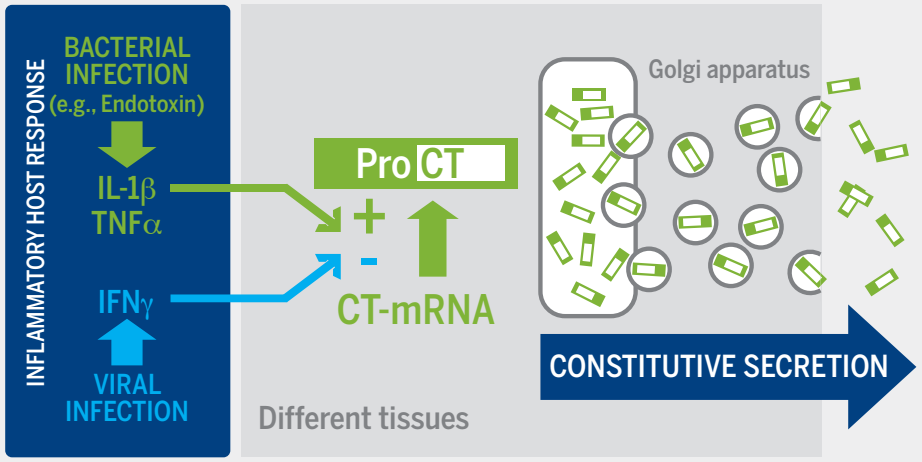



**Figure 2: Schematic diagram of the regulation of CALC-I gene expression leading to PCT release in cells during septic conditions.**
Adapted from Muller, B, et al. *J Clin Endocrinol Metab.*[6]

**Procalcitonin is up-regulated in response to bacterial but not viral infections, making it a more specific biomarker for bacterial infections.**

## 3. Different cut-offs in different clinical settings

The probability for the presence of a severe bacterial infection correlates with increasing levels of circulating PCT:

- the higher the PCT level, the higher the risk that a patient has sepsis due to a bacterial infection.
- the higher the PCT level, the more severe the underlying infection.
- the lower the PCT level, the lower the risk for a serious bacterial infection and the higher the probability that these patients may instead have mild non-bacterial infections.

**For optimal performance, PCT cut-off values should be adapted to patient acuity (risk level) and clinical setting.[7]**

- in low-acuity patients **(Figure 3A),** typically those with respiratory tract infections presenting to an emergency department (ED), a PCT cut–off of ≤ 0.25 ng/mL or 0.1 ng/mL has a very high negative predictive value to exclude a serious bacterial infection. Non-bacterial infections, such as bronchitis or viral-induced exacerbation of Chronic Obstructive Pulmonary Disease (COPD), are much more likely.
- in high-acuity patients **(Figure 3B),** typically those transferred to the intensive care unit (ICU), PCT cut–offs of 0.5 ng/mL or ≥ 0.26 ng/mL should be used. PCT levels below these cut-offs make severe bacterial infections and sepsis very unlikely and other diagnoses explaining the patients' medical conditions should be considered.

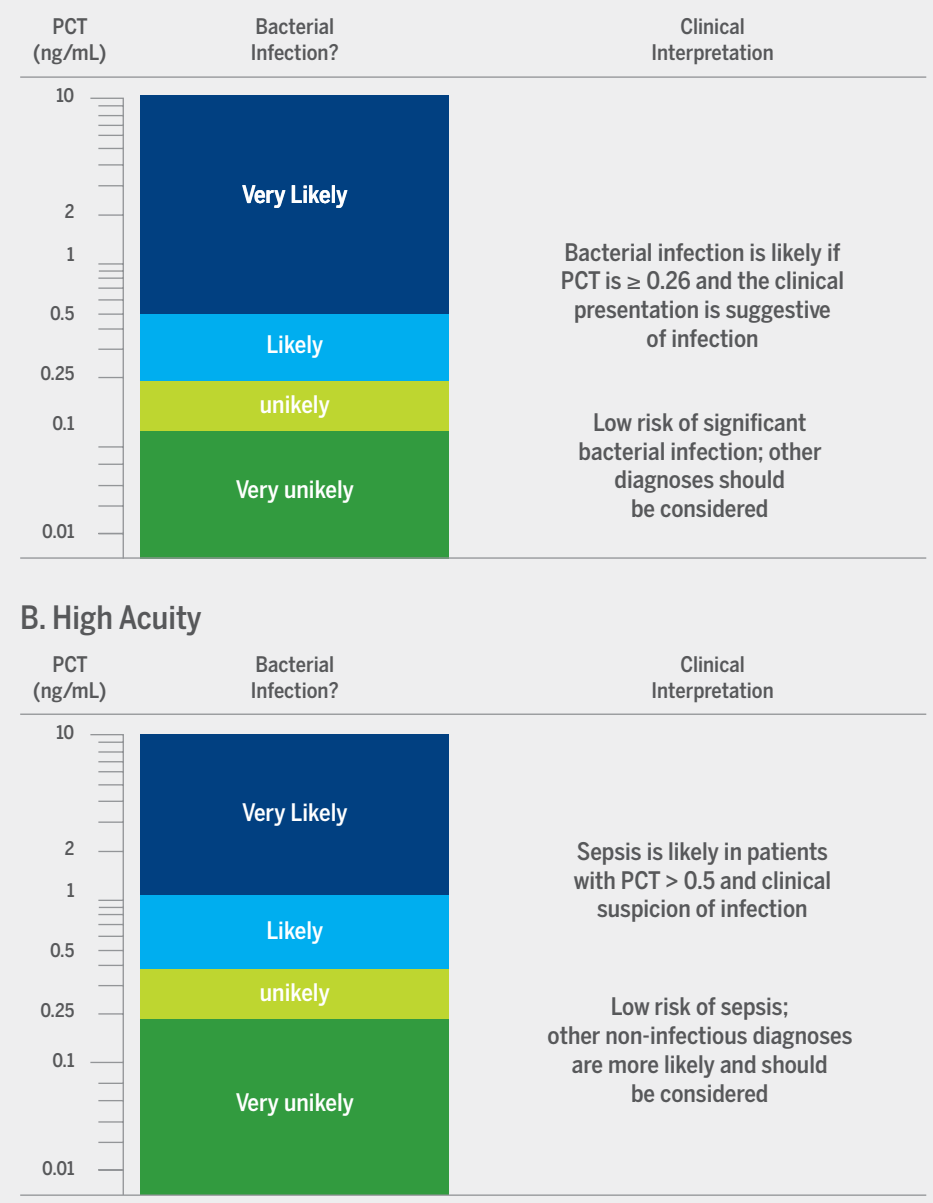



**Figure 3: PCT cut-off levels adapted to acuity. Low acuity refers to patients typically seen in the ED without clinical signs of severe infection or sepsis. High acuity refers to patients transferred to the Intensive Care Unit because of severe disease.**

Adapted from Schuetz P, et al. *BMC Med.*[5] and Albrich WC, et al. *Arch Intern Med.*[8]

# II – DIAGNOSTIC AND PROGNOSTIC USE OF PROCALCITONIN

## 1. Influence of non-bacterial and different types of bacterial infections on PCT levels

Since PCT is mainly up-regulated in bacterial infections, it helps to **distinguish non-bacterial from bacterial infections.** In respiratory infections, PCT remains low (in the range of healthy subjects) in patients with the clinical diagnosis of bronchitis – which is a viral infection. Yet it significantly increases in patients with bacterial pneumonia.[9]

Clinical studies have shown no additional benefit of antibiotic treatment in ED patients and out-patients with clinical signs of a respiratory infection and low PCT levels.[10,11] This indicates that, in this population, a **low PCT level is helpful to rule out bacterial infections** requiring antibiotic therapy.[10,11]

Traditional culture methods, such as blood cultures, focus on identification and characterization of pathogens. This is important for deciding which antibiotics should be used and to understand resistance patterns. They do not, however, inform about the **host response** to the infection, which depends on the virulence of the micro-organism and the severity of infection. PCT, on the other hand, mirrors the patient's response to the infection and therefore (indirectly) to the extent and severity of infection. With new microbiological methods becoming available that rapidly identify micro-organisms with higher sensitivity, **PCT may help to increase specificity** of these methods by providing information about the severity and "relevance" of microbial culture results in individual patients.[10,11]

In line with this, PCT has been shown to be helpful in differentiating true infection from contamination in patients with growth of coagulase-negative staphylococci in their blood cultures.[12]

- **PCT helps in the differentiation of non-bacterial from bacterial infection and the correct interpretation of microbiological test results.**
- **PCT also provides additional information about the host response to the infection.**

PCT may also help to accurately **predict the risk for bacteremic infection defined by blood culture positivity.** PCT was found to be significantly increased in bacteremic patients presenting with community-acquired pneumonia (CAP). In a clinical study, < 1% of patients had positive blood culture when their initial PCT level was ≤ 0.25 ng/mL, which increased to > 20% in patients with PCT > 2.5 ng/mL.[13] However, it seems that PCT may not help to reliably predict the type of bacterial micro-organism. In fact, a German study found that a high PCT level was a strong indication of infection of bacterial origin; however, the result did not indicate the type of bacteria (Gram-positive / Gram-negative).[14]

**Procalcitonin is not a substitute for microbiological tests. It does not identify micro-organism type or provide resistance patterns.**

PCT is therefore better considered as a **measure of a patient's response to infection** and indirectly the extent and severity of infection. It helps to estimate the likelihood of a relevant bacterial infection; with increasing PCT concentrations, a relevant and serious bacterial infection becomes likely. Conversely, an alternative diagnosis becomes more likely if PCT levels remain low.[13]



## 2. Diagnostic value of procalcitonin in the early recognition of sepsis

Globally, an estimated 30 million cases of sepsis occur each year, with more than 6 million cases of neonatal and early childhood sepsis, and the rate of sepsis mortality remains unacceptably high (between 30 and 60% of patients with sepsis die).[15] Furthermore, sepsis has significantly increased by an annual rate of 8-13% over the past decade due to the aging population, the development of drug-resistant and more virulent varieties of pathogens, and (in the developing world) to malnutrition, poor sanitation, and lack of access to vaccines and timely treatments.[16]

1 out of every 23 patients in the hospital has sepsis.

The cornerstone of today's sepsis treatment is **early recognition of the condition and early initiation of appropriate antibiotic therapy,** as well as fluid resuscitation. Clinical signs, however, such as the systemic inflammatory response syndrome (SIRS) criteria, lack both sensitivity and specificity. Therefore,blood biomarkers (such as PCT) that mirror the severity of bacterial infectionsimprove the early diagnosis of sepsis.[2,17]

PCT has been demonstrated to be most clinically useful, and superior to commonly used clinical variables and laboratory tests, in the **early diagnosis** of sepsis.[2] Moreover, it has been shown to correlate with the extent and severity of microbial invasion. Simply put, **PCT improves the clinical work-up of patients with suspicion of sepsis.[17]**

- **In the ED setting,** low PCT values (≤ 0.25 ng/mL) in patients with clinical signs of infection indicate a low probability for bacterial infection and sepsis.[5] Usually PCT levels are found to be > 0.5 ng/mL or higher if patients have bacterial infections leading to sepsis. **(Figure 4)**

- **In the ICU setting and in patients with suspicion of sepsis or septic shock,** PCT levels are usually found to be higher than 2 ng/mL. A PCT level of < 0.5 ng/mL, however, makes sepsis very unlikely (high negative predictive value).[17] **(Figure 5)**

PCT therefore enables the diagnostic differentiation between various clinical conditions mimicking severe systemic bacterial infections and sepsis. Refer to p. 35 for new sepsis definitions.

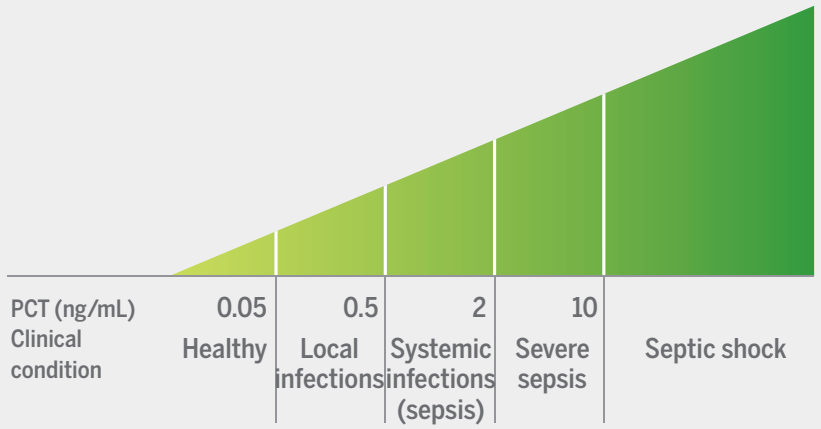
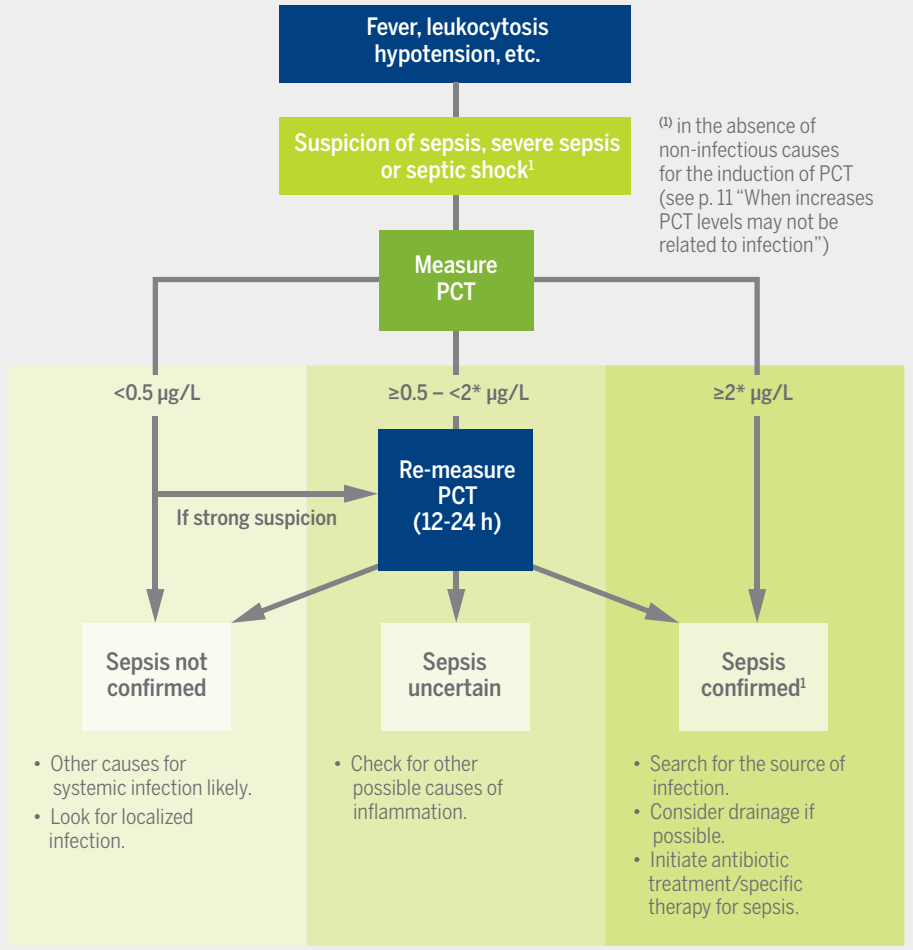



**Figure 4: Increasing PCT levels reflect continuous progression from a healthy condition to sepsis and septic shock**

Adapted from Meisner M, et al. *J Lab Med*.[18]

## Sepsis diagnosis with PCT




* The cut-off of 2 µg/L given in the scheme is for orientational purposes only. Each clinical department should adapt it according to its patient population. [Cut-off may be at PCT level higher or lower than 2 µg/L, depending on patient's background, e.g., major surgery (higher) or patient in medical ICU (lower).]

**Figure 5: Sepsis diagnosis with PCT in ICU setting**

Adapted from Harbarth S, et al. *Am J Resp Crit Care Med*.[17]

**Procalcitonin is most promising for early detection of patients at risk for sepsis and bacteremia:**

- **Low procalcitonin levels may help to rule out sepsis and help physicians focus on other medical conditions.**
- **High PCT levels confirm that sepsis is very likely.**

## 3. Prognostic value of procalcitonin in the ED and ICU

The **Procalcitonin Monitoring Sepsis Study (MOSES)** completed in the US showed that sustained elevated PCT levels are an independent risk factor for mortality. PCT levels that decline less than 80% from the baseline within four days are associated with increased all-cause mortality—especially when the baseline PCT measurement is greater than 2.0 ng/mL. **(See Figure 7 on p. 18)**

PCT has prognostic implications because **levels correlate with severity of infection,** and more importantly, **a decrease of PCT over 24-48 hours** suggests clinical recovery and **favorable patient outcomes.**

The following interpretation of PCT results based on clinical evidence has been suggested [19]:

- **in low-acuity patients with respiratory infections:**

  a) A **low PCT level** identifies patients at lower risk for a bacterial etiology and CAP and thus low mortality.
  b) A **high PCT level** identifies patients at higher risk for a bacterial etiology and CAP and, perhaps, higher mortality.

- **in a high-acuity population:** PCT levels < 0.1 ng/mL effectively decrease the likelihood of mortality from a bacterial etiology and other non-bacterial pathologies should be aggressively sought.



- **The assessment of PCT kinetics over time** is more helpful than initial values in moderate and higher risk patients **(Figure 6).** Levels failing to decline during initial follow-up identify patients not responding to therapy.

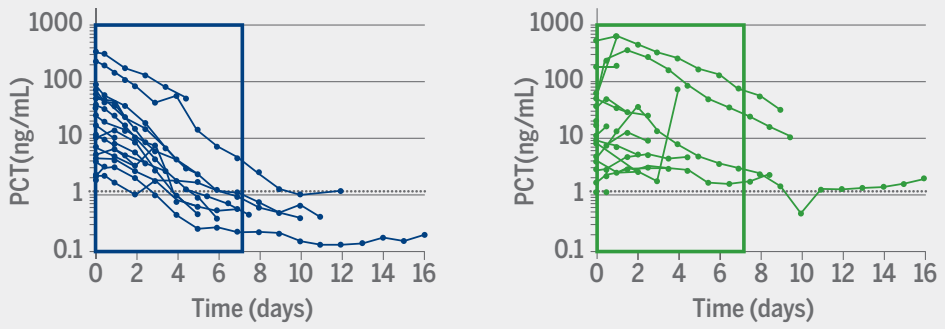



**Figure 6. Daily variations of PCT levels during ICU hospitalization in patients admitted with severe sepsis and septic shock that survived or did not survive.**
Adapted from Harbarth S, et al. *Am J Respir Crit Care Med.*[17]

**MOSES** has helped expand the clinical utility of PCT. In this study, PCT is used to help assess the response of septic patients to treatment by comparing a baseline PCT measurement with a PCT value taken on Day Four.[20] Monitoring the change in PCT over time, in conjunction with other laboratory findings and clinical assessments, helps assess the cumulative 28-day risk of mortality for patients with sepsis or septic shock who are admitted to the ICU. The key findings of this major multi-site US study included:

- Changes in PCT levels over time improve prediction of the cumulative 28-day risk of all-cause mortality for patients diagnosed with sepsis or septic shock.
- In patients with a decrease in PCT < 80% during the first four days following diagnosis of sepsis or septic shock, a two-fold increased risk of death was observed, compared to those who experienced a decrease in PCT > 80%.

- The initial PCT level (≤ 2.0 ng/mL or > 2.0 ng/mL) provided important additional information about the mortality risk when reassessing the patient's clinical course using PCT measurements on subsequent days.

Assessing PCT kinetics over time provides valuable information regarding:

- Patient disposition
- Response to treatment
- Likelihood of survival

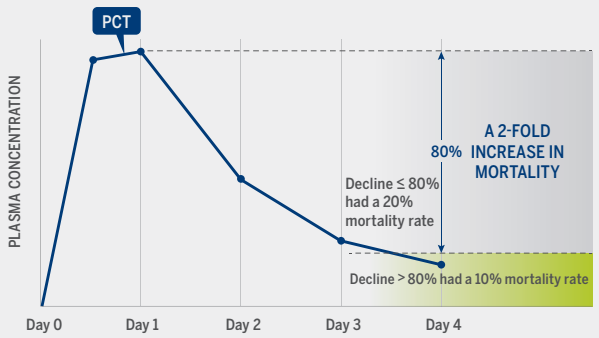



**Figure 7. Unique kinetics of PCT are strong indicators of mortality risk over time.**

Adapted from Schuetz P, et al. *Crit Care.*[20]

**The best prognostic information is derived from monitoring PCT levels over time:**

- **Decreasing levels are found in patients responding to antibiotic therapy.**
- **Non-decreasing levels may point to treatment failure.**

## 4. Use of procalcitonin in pediatrics

PCT is a very useful biomarker in the pediatric population. The recent NeoPIns study found that PCT-guided decision-making significantly shortened the duration of antibiotic therapy in newborns with suspected early-onset sepsis.[21]

The ProPAED study showed that PCT-guided therapy significantly reduced antibiotic exposure in children and adolescents with Lower Respiratory Tract Infections (LRTI).[21]



In association with clinical signs, it can help physicians in the following situations:

- **Early differentiation**
  A PCT cut-off of 0.5 ng/mL has been suggested to enable early differentiation of serious bacterial infection and non-severe or non-bacterial infections in children with fever without source.[22]
- **Risk indexing**
  The Lab-score – a risk index score associating CRP, procalcitonin and urinary dipstick – also seems to be a useful tool to predict Severe Bacterial Infection (SBI, or sepsis).[22]
- **Prediction of pneumococcal pneumonia**
  Elevated PCT and CRP in combination with a positive pneumococcal urinary antigen are reliable predictors of pneumococcal pneumonia.[23]
- **Antibiotic guidance**
  In a randomized controlled trial, Baer et al. demonstrated that although PCT guidance did not reduce initial initiation of antibiotics, it did reduce antibiotic exposure in children and adolescents with LRTI, by reducing the duration of antibiotic treatment by almost 2 days (4.5 days in PCT group vs. 6.3 days in control group).[24] This effect was most pronounced in pneumonia patients (9.1 days in PCT group vs 5.7 days in control patients).[24]

A retrospective analysis of PCT concentrations from the **EPIC** study (CDC: Etiology of Pneumonia in the Community) of children hospitalized with radiographically confirmed CAP demonstrated that lower PCT concentrations were associated with a reduced risk of atypical detection and may help identify children who would not benefit from antibiotic treatment.

Multivariable regression was used to assess associations between PCT concentrations and etiology and severity. Among 532 children, patients with typical bacteria had higher PCT concentrations. No child with PCT < 0.1 ng/mL had typical bacteria detected. Procalcitonin of < 0.25 ng/mL featured a 96% negative predictive value in this analysis.[25]

# III – USING PCT TO GUIDE ANTIBIOTIC THERAPY DECISIONS

Emerging antimicrobial resistance, and the lack of new antibiotics in development to meet the challenge of multi-drug resistance, makes the **most prudent use of existing antibiotics** crucial for preserving their efficacy. Additional efforts are required to **reduce the unnecessary and prolonged use of antibiotics** in self-limiting non-bacterial and resolving bacterial infections.

PCT's demonstrated efficacy in different clinical settings — as a tool to help **guide decisions to start, continue or stop antibiotic therapy,** based on initial PCT levels and repeated measurements – contributes to **efficient antibiotic stewardship.**[4,7]

## 1. Use of procalcitonin in ED and in-patients

### i. LRTI patients (Bronchitis, COPD exacerbation, CAP) in the ED

Bronchitis or exacerbation of COPD is very often a viral infection. Nevertheless, patients are still often being over-treated with antibiotics, because it is difficult to rule out a bacterial etiology based on clinical grounds.

Studies have evaluated PCT protocols in these patients and found that for patients who are clinically stable and are treated at the ED or are hospitalized, the **initiation of antibiotic therapy** should be based on **clinical grounds and a PCT value of ≥ 0.26 ng/mL.**[10]

- If **PCT remains lower, antibiotics can be withheld** and patients can be reassessed clinically without safety concerns.
- If patients are clinically stable, an alternative diagnosis should be considered
- If patients are unstable, then antibiotics may be considered.
- If patients do not improve in the short follow-up period (6-12 hours), clinical reevaluation and remeasurement of PCT is recommended **(See Figure 10 on p. 25).**

This concept has been investigated in different trials including more than 1,000 patients with bronchitis and COPD exacerbation. These studies have shown that **unnecessary antibiotic use was decreased by 50% in bronchitis patients and 65% in COPD patients** with similar outcomes in terms of survival, risk for ICU admission or disease specific complications, recurrence of infection, and lung function (FEV1) recovery.[4]

- **Patients with bronchitis or COPD exacerbation and low PCT levels do not require antibiotic therapy, if no over-ruling condition is present.**
- **In severe COPD, empiric therapy may still be considered initially in high-acuity patients.**

### ii. Community Acquired Pneumonia in the ED

Based on these trials, a **PCT level ≥ 0.26 ng/mL** strongly suggests that a **bacterial infection is likely** and **antibiotic therapy should be rapidly initiated**. If PCT testing is available within 1-2 hours of presentation, the decision to initiate antibiotics may be assisted by the initial PCT level. In other settings, where PCT testing may be delayed, initiation of antibiotics should be based on clinical suspicion, with the decision to discontinue antibiotics dependent on a PCT level. For patients in whom antibiotics are initiated, PCT should be reassessed every 2 days to monitor the course of treatment. **Antibiotics may be safely discontinued if a patient shows clinical recovery and PCT decreases to ≤ 0.25 ng/mL (or greater than 80% from the peak level).**[10]

Such protocols have resulted in an **important reduction in antibiotic exposure of 40%** without negatively affecting clinical outcomes and without increasing the risk for recurrent infections **(Figure 8).**

Highly increased PCT levels in this situation make bacteremic disease more likely and argue that the infection may be more severe than expected based on clinical signs and symptoms.[4]

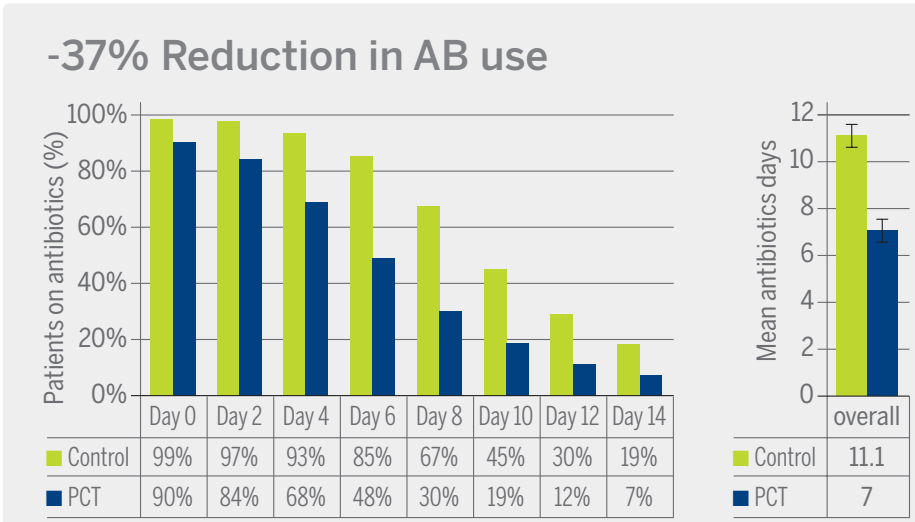



**Figure 8: Antibiotic use in CAP patients with (green) and without (grey) PCT guidance.**

Adapted from Schuetz P, et al. *Clin Infect Dis*.[4]

**With PCT guidance, patients were treated for a mean of 7 days compared to 11.1 days in the control group, indicating a reduction in antibiotic exposure of around 40%. (See Figure 6 on p. 17)**

**In patients suspected of having pneumonia** based on the presence of infiltrates, a **consistent (over 24-48 hours) PCT level of < 0.1 ng/mL** or even 0.1 ng/mL to ≤ 0.25 ng/mL **argues against a typical bacterial infection.** Physicians should then consider other conditions in their differential diagnosis, such as pulmonary embolism, acute heart failure (AHF), bronchiolitis obliterans organizing pneumonia (BOOP), *Pneumocystis jiroveci pneumonia* (PJP), and viral pneumonia. Particularly during flu season, influenza may be an important diagnosis to consider.[4]



If antibiotics are withheld, reassess if symptoms persist/worsen, and/or repeat PCT measurement within 6-24 hours. If PCT levels are ≤ 0.25 ng/mL, but bacterial infection is still highly suspected based on the clinical presentation or microbiological results, antibiotic therapy may still be considered, particularly in patients at higher risk for adverse outcome. **If PCT remains low during follow-up, early discontinuation of antibiotics should be considered as well as an aggressive diagnostic workup for other etiologies (Figure 9A).[7]**

The **proHosp Study (Procalcitonin Guided Antibiotic Therapy and Hospitalization in Patients With Lower Respiratory Tract Infections)** was designed to examine whether a PCT algorithm can reduce antibiotic exposure without increasing the risk for serious adverse outcomes in patients with acute LRTI.[10]

In patients with LRTI, a strategy of PCT guidance compared with standard guidelines resulted in similar rates of adverse outcomes, as well as lower rates of antibiotic exposure and antibiotic-associated adverse effects.[26]

**Decision-making on initiation of antibiotic therapy for patients with**

| PCT Result | < 0.10 ng/mL | 0.10-0.25 ng/mL | 0.26-0.50 ng/mL | > 0.50 ng/mL |
|---|---|---|---|---|
| Interpretation | Antibiotic therapy strongly discouraged. Indicates absence of bacterial infection. | Antibiotic therapy discouraged. Bacterial infection unlikely. | Antibiotic therapy encouraged. Bacterial infection possible. | Antibiotic therapy strongly encouraged. Suggestive of presence of bacterial infection. |
| Follow-up | For in-patients, if antibiotics are withheld, repeat PCT measurement within 6-24 hours. For outpatients, reassess and/or repeat test if symptoms persist/worsen. In all cases, antibiotic therapy should be considered regardless of PCT result if the patient is clinically unstable, is at high-risk for adverse outcome, has strong evidence of bacterial pathogen, or the clinical context indicates antibiotic therapy is warranted. | | Follow up samples should be tested at regular intervals and antibiotic therapy may be adjusted using the discontinuation table in Figure 10a. | |

**Figure 9: Decision-making on initiation of antibiotic therapy for patients with suspected of confirmed LRTI.**

Adapted from Albrich WC, et al. *Arch Intern Med.*

**Decision-making on discontinuation of antibiotics in patients with LRTI:**

**Antibiotic therapy may be discontinued if $PCT_{Current}$ is ≤ 0.25 ng/mL or if the ΔPCT > 80%**

- $PCT_{Peak}$: Highest observed PCT concentration.
- $PCT_{Current}$: Most recent PCT Concentration.
- ΔPCT: Calculate by using the following equation:

$$\Delta PCT = \frac{PCT_{Peak} \text{ [ ]} - PCT_{Current} \text{ [ ]}}{PCT_{Peak} \text{ [ ]}} \times 100\%$$

Antibiotic therapy may be continued based upon other clinical findings, such as apparent progression on chest x-ray or ongoing/increasing toxicity.

**If PCT remains high, consider treatment failure.**

**Figure 9A: Decision-making on discontinuation of antibiotic therapy for patients with suspected of confirmed LRTI.**

From package insert for VIDAS® B•R•A•H•M•S PCT™ (30450-01).

**In community-acquired pneumonia (CAP), monitoring the course of PCT helps shorten the duration of treatment. A PCT-guided strategy therefore has important clinical and epidemiological implications: helping to prevent the selection of resistant bacteria and reducing the risk of cross-contamination, as well as decreasing treatment costs.[27]**



## 2. Use of procalcitonin in critical care

**An initially low PCT level makes other, non-infectious differentiated diagnoses more likely. Monitoring the course of PCT helps physicians to safely reduce duration of therapy. However, timely empiric antibiotic therapy should always be considered in ICU patients with sepsis.**

**Decision making on antibiotic discontinuation for suspected or confirmed septic patients:**

After the initiation of antibiotic therapy for suspected or confirmed septic patients, follow-up samples should be tested at regular intervals, such as every 1-2 days, to assess treatment success and to support a decision to discontinue antibiotic therapy. The frequency of follow-up testing should be at physicians' discretion, taking into account the patients' evolution and progress, and using the subsequent PCT results [28]:

**Antibiotic therapy may be discontinued if $PCT_{Current}$ is ≤ 0.50 ng/mL or if the ΔPCT > 80%**

- $PCT_{Peak}$: Highest observed PCT concentration.
- $PCT_{Current}$: Most recent PCT concentration.
- ΔPCT: Calculate by using the following equation:

$$\Delta PCT = \frac{PCT_{Peak} \text{ [ ]} - PCT_{Current} \text{ [ ]}}{PCT_{Peak} \text{ [ ]}} \times 100\%$$

Antibiotic therapy may be continued based upon other clinical findings, such as apparent progression on chest x-ray failure to control a local infection or ongoing physiologic instability. Antibiotic therapy may be discontinued if a patient shows clinical improvement and current PCT level has dropped by 80% from baseline and/or is ≤ 0.50 ng/mL

**If PCT remains high, consider treatment failure.**

**Figure 10: Decision making on antibiotic therapy discontinuation for patients with suspected of confirmed sepsis.**

Adapted from package insert for VIDAS B•R•A•H•M•S PCT (30450-01).

**i. Sepsis in the ICU**

The **Stop Antibiotics on Procalcitonin guidance Study (SAPS)** published in 2016 is the largest randomized interventional multicenter trial conducted to date that assesses the utility of PCT for antibiotic stewardship in critically ill adults.[31]

The study showed that low PCT concentrations help physicians to stop antibiotics earlier in patients with initial suspicion of infection – thereby supporting more adequate diagnosis and treatment, which are the cornerstones of antibiotic stewardship.[3]

Importantly, PCT guidance resulted in a **decrease in mortality from 27% to 21% at Day 28,** which remained robust in the long-term follow up after 1 year.[3]

A recent literature review by Carr, et al. addressed the benefits of using PCT in different ICU settings as a guide to appropriate termination of antibiotics and cost savings.[31]

The review found that a **PCT level ≥ 2.0 ng/mL is most sensitive and specific for sepsis** and that a **PCT level < 0.5 ng/mL is safe to stop antibiotics in septic ICU patients.[30]**

The review also supports the use of PCT-based algorithms, such as those recommended by or adapted from Schuetz, et al.[7]

- A patient with a **systemic inflammatory response and an initial PCT level < 0.5 ng/mL** is very unlikely to have an infectious etiology of the SIRS response, and **antibiotics can be stopped earlier.[3]** In this case, other diagnoses should be considered, including viral etiologies.



- In critically ill patients, **a strong suspicion of severe bacterial infection with a PCT level > 2 ng/mL** are diagnostic of sepsis and have a high Positive Predictive Value (high specificity), and **antibiotic therapy should be started immediately.[3]** Careful clinical evaluation and periodic monitoring (every 1-2 days) of PCT levels after antibiotic initiation is an appropriate strategy in these patients.[7] **(Figure 11)**.

## DISCONTINUATION USING PCT KINETICS

PCT less than or equal to 0.5 ng/mL
— or —
Decline from baseline of greater than 80%

- **A drop of PCT to ≤ 0.5 ng/mL (or greater then 80%** from peak values) appears to be an acceptable and safe threshold for **stopping antibiotic therapy,** assuming patients also show a favorable clinical response.[3,7]
- **If PCT levels do not decrease by greater than 80% at Day 4, treatment failure should be considered** and patient re-assessment is recommended.[7]

The use of PCT to decide when to **stop antibiotics based on a level < 0.5 ng/mL** in patients with pulmonary infections and/or sepsis has been shown to **reduce total antibiotic usage and decrease the duration of antibiotics**.[3]

In a systematic review including more than 500 patients from the medical and surgical ICU, such protocols have been shown to **reduce antibiotic therapy duration from a median of 12 to a median of 8 days**, with similar outcomes in patients and, in some studies, reduced length of ICU stays.[7]

**ii. Community-acquired pneumonia in the ICU**

Antimicrobial overuse in ICU patients with non-bacterial pneumonia caused by influenza A(H1N1) could be significantly reduced if antibiotic treatment could be limited only to patients with a true community-acquired respiratory co-infection (CARC).[29]

Procalcitonin has been found to be a helpful marker in excluding influenza in ICU patients with pneumonia. A recent study by Rodriguez, et al. showed that low serum levels of PCT in patients admitted to the ICU with confirmed influenza A(H1N1) infection and without shock were an accurate predictor for ruling out the presence of CARC (< 6%).[29]

Moreover, in this study, **PCT was found to be more accurate than CRP.**

**iii. Infectious complications in surgical ICU patients**

For patients with suspicion of infection in the post-operative course after major surgery or trauma, the use of a blood biomarker such as PCT may be limited, as **biomarker levels may reflect the cytokine response to the injury** and not necessarily point to an underlying infection. In this situation, the kinetics of the biomarker is much more important than initial post-operative values, as is the case for PCT.

- **In post-surgical patients,** PCT levels increase immediately due to surgical stress, but a rapid decrease (50% every other day) should be observed in uncomplicated surgery.
- **If PCT continues to increase** after 24 hours or only decreases slowly, the post-operative course is likely to be complicated by an infection. **(Figure 11).**[30]

**Monitoring of PCT during the post-operative course therefore provides useful information to physicians.**

Studies have suggested that PCT is helpful for **differentiation of infectious from non-infectious causes of fever** after orthopedic surgery.[31]

- A spike in PCT levels 3-4 days post-operatively or following trauma may indicate a **secondary bacterial infection.**



- If antibiotics are started in the post-operative course based on clinical suspicion, monitoring PCT **facilitates early discontinuation of antibiotics** in patients showing a favorable clinical response and a drop of PCT levels.[32]

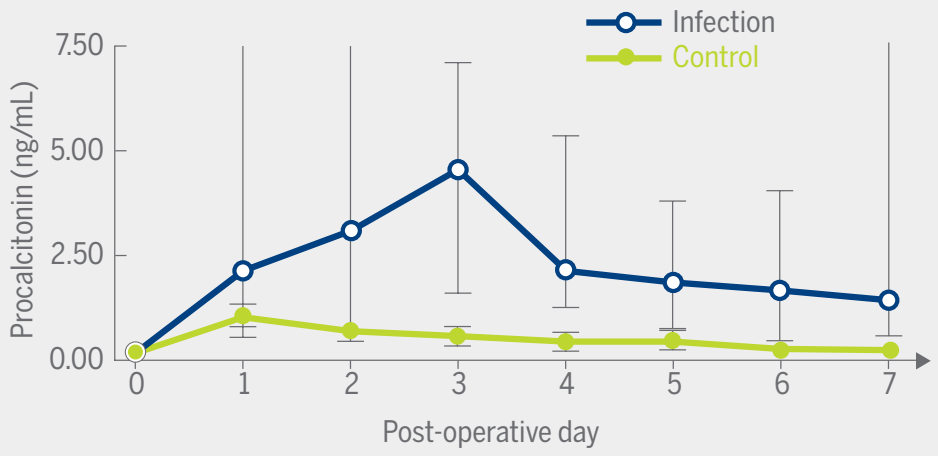



**Figure 11: Comparison of PCT in patients with complicated (infection) and uncomplicated post-operative courses.**

**Monitoring PCT in the post-operative phase is helpful for early identification of complications and to guide antibiotic duration.**

EXAMPLE:

### Value of monitoring PCT in post-operative patients

Making the decision for relaparotomy after secondary peritonitis is difficult, but **early control of a persistent intra-abdominal infectious focus is crucial.** Early identification of a persistent or recurrent infection solely by clinical parameters, or an inflammatory biomarker such as C-reactive protein, is limited in the first 48 hours after an initial operation because of the confounding effects of operative trauma, anesthesia, and the concomitant need for artificial ventilation, sedation, and analgesia.

Clinical studies have shown that **monitoring PCT levels** in this situation **improves risk assessment,** as a significant decrease in PCT serum levels was observed in patients with successful operative eradication of the infectious focus with the initial laparotomy. In patients with a persisting infectious focus, however, the serum PCT did not decrease.

**A ratio of Day 1 to Day 2 PCT of > 1.03 has been suggested to be highly indicative of unsuccessful elimination of the septic focus.**[33]



## IV – FREQUENTLY ASKED QUESTIONS

**1. Is there an international standard for procalcitonin assays?**

Several procalcitonin (PCT) assays exist in the market today. All B•R•A•H•M•S PCT™ assays meet the highest international quality standards, use the original raw material from B•R•A•H•M•S GmbH, are calibrated on the same standard, and offer excellent correlation and concordance at the established clinical cut-offs. In case of patient follow-up, it is recommended to use the same PCT assay technique.

**2. Can procalcitonin be falsely high in the absence of bacterial infection or falsely low in the presence of bacterial infection?**

- **Non-specific elevations** of PCT levels in the absence of a bacterial infection can typically be seen in situations of massive stress, e.g., after severe trauma, cardiac shock, or surgery. In these situations, PCT values are usually only moderately elevated and show a rapid decline in follow-up measurements.
- Conversely, **falsely low PCT levels,** typically seen during the early course or in localized infections (i.e., empyema) often show an increase in the follow-up measurements. In these cases, subtle increases of PCT may already point to an underlying infection. Therefore, **highly sensitive PCT assays are required,** as subtle changes of PCT at very low concentrations can be monitored, increasing the test's sensitivity and therefore patient safety.

### 3. Clinical limitations

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

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

- neonates < 48 hours of life (physiological elevation)[34]
- acute respiratory distress syndrome
- first days after major trauma, major surgical intervention, severe burns, treatment with OKT3 antibodies and other drugs stimulating the release of pro-inflammatory cytokines[35]
- invasive fungal infections or acute attacks of *Plasmodium falciparum*[36,37]
- prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, small cell lung cancer, medullary C-cell carcinoma of the thyroid[35]

**LOW PCT levels do not automatically exclude the presence of bacterial infection**

Low PCT levels may be obtained during the early course of infections, in localized infections and in sub-acute endocarditis. Follow-up and re-evaluation of PCT in clinical suspicion of infection or persisting symptoms is therefore essential.

**PCT levels should be integrated in clinical algorithms and used in conjunction with a thorough clinical assessment.**

### 4. Is PCT testing cost-effective?

An important consideration when using a new diagnostic test is the associated costs relative to the potential for generating other care-related cost savings.



Several studies have shown that **PCT in the critical care setting (ICU) is cost-effective if used to guide antibiotic decisions** due to the high antibiotic costs associated with critically ill patients.[38-41]

An extensive retrospective US-database analysis of the clinical and cost impact of PCT testing in the ICU found that PCT-guided care is associated with lower costs as well as reduced length of stay, and demonstrated the value and impact of PCT use in real-world clinical practice. An average cost-saving of $2,759 per PCT-treated patient was observed.[70]

A recent health-economics study of PCT-guided antibiotic treatment of Acute Respiratory Infections (ARI), based on an individual patient data meta-analysis showed substantial savings in common US healthcare settings.[39] The study concluded that PCT-guided care is associated with net savings ranging from $73,326 in the ICU to > $5 million in the outpatient and ED settings, for **total savings of more than $6 million without negative impact on treatment outcomes**.

Importantly, secondary costs due to side effects and emergence of antibiotic resistance should also be considered. These effects are found not only on a patient level, but also on a population level.

In addition, sepsis is costly. A 2015 report has confirmed sepsis as being responsible for the most readmissions to a hospital within 30 days after a hospital visit. The life-threatening and often misunderstood condition is also the most expensive diagnosis, leading to readmissions costing more than $3.1 billion per year.[40] Cost-effective diagnostic solutions can therefore contribute significantly to reducing the cost of sepsis.

**Cost benefits of using PCT include reduced antibiotic exposure and risk for side-effects, shorter length of stay, and reduced emergence of multi-drug resistant bacteria.**

**5. How is PCT used in patients on hemodialysis?**

A high level of PCT and an increase (or failure to decrease) over time could be a strong indicator of bacterial infection in hemodialysis patients.[42] This study showed that PCT levels should be determined before hemodialysis with a recommended cut-off of 0.5 ng/mL in this population. However, this new PCT application should be validated in more extensive clinical trials.

## GUIDELINES AND RECOMMENDATIONS

The fourth edition of the Surviving Sepsis Campaign (SSC) Guidelines published in 2016 advocates that a low PCT level helps to rule out an infection in patients with systemic inflammatory response syndrome (SIRS). The Guidelines *"suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients...."*[43] In 2015, the **SSC Care Bundles** were revised in response to new evidence regarding use of central line catheters in the 6-hour bundle.[44]

## New Definitions for Sepsis and Septic Shock

**Based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) Singer M, et al. *JAMA*.[45]**

In 2016, new definitions of sepsis and septic shock were published. In addition, the notion of Systemic Inflammatory Respiratory Syndrome (SIRS) was abandoned, since it was not considered to be sensitive or specific enough, and the term severe sepsis was considered redundant.

**Sepsis** is now defined as **life-threatening organ dysfunction caused by a dysregulated host response to infection**. Organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality > 10% **(Figure 12)**.

**Septic shock** is defined as a **subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone**. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of **≥** 65 mm Hg and serum lactate level > 2 µmol/L (> 18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates > 40%.

**A new bedside clinical score – the quickSOFA (qSOFA) score** – has been established to support rapid identification of potentially septic patients in out-of-hospital, emergency department, or general hospital ward settings **(Figure 14)**. Adult patients with suspected infection can be rapidly identified as more likely to have poor outcomes typical of sepsis if they have at least **2 of the following clinical criteria:**

- **respiratory rate of > 22/min**
- **altered mental state**
- **systolic blood pressure of < 100 mm Hg**

| | SCORE | | | | |
|---|---|---|---|---|---|
| **SYSTEM** | **0** | **1** | **2** | **3** | **4** |
| RESPIRATION | | | | | |
| $PaO_2/FIO_2$, mmHg (kPa) | ≥ 400 (53.3) | < 400 (53.3) | < 300 (40) | < 200 (26.7) with respiratory support | < 100 (13.3) with respiratory support |
| COAGULATION | | | | | |
| Platelets, $\times 10^3/\mu L$ | ≥ 150 | < 150 | < 100 | < 50 | < 20 |
| LIVER | | | | | |
| Bilirubin, ng/dL (µmol/L)L | < 1.2 (20) | 1.2-1.9 (20-32) | 2.0-5.9 (33-101) | 6.0-11.9 (102-204) | >12.0 (204) |
| CARDIOVASCULAR | MAP ≥ 70 mm Hg | MAP < 70 mm Hg | Dopamine < 5 or dobutamine (any dose)[b] | Dopamine 5.1-15 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1[a] | Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1[a] |
| CENTRAL NERVOUS SYSTEM | | | | | |
| Glasgow Coma Scale score[b] | 15 | 13-14 | 10-12 | 6-9 | < 6 |
| RENAL | | | | | |
| Creatinine, ng/dL (µmol/L) | < 1.2 (110) | 1.2-1.9 (110-170) | 2.0-3.4 (171-299) | 3.5-4.9 (300-440) | > 5.0 (440) |
| Urine output, mL/d | | | | < 500 | < 200 |

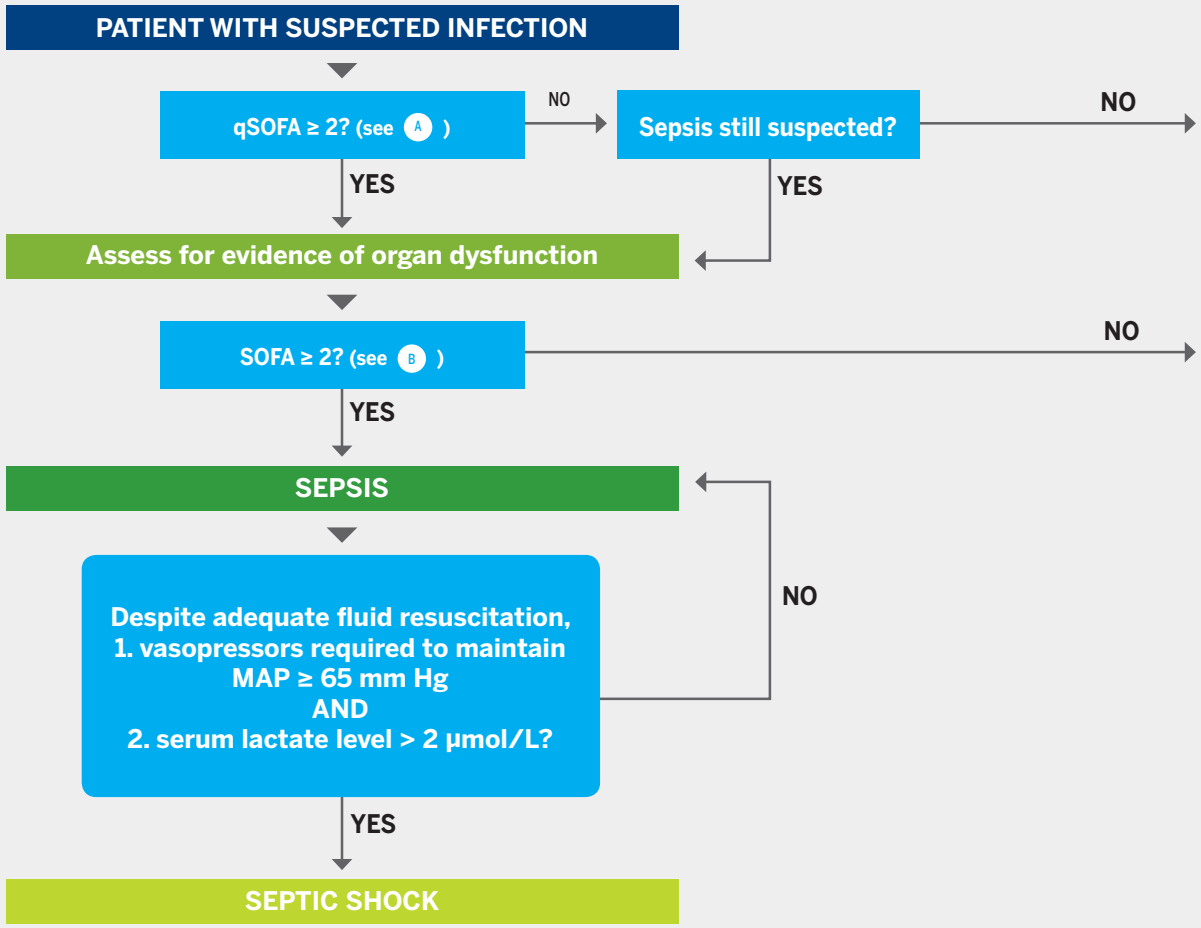
Abbreviations: $FIO_2$, fraction of inspired oxygen; MAP, mean arterial pressure; $PaO_2$, partial pressure of oxygen. Sequential (Sepsis-Related) Organ Failure Assessment Score.[a]

[a] Catecholamine doses are given as µg/kg/min for at least 1 hour.

[b] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

**Figure 12. Sequential (Sepsis-Related) Organ Failure Assessment (SOFA Score)**

Adapted from Singer M, et al. *JAMA.*[45]




**A**

### qSOFA Variables

- Respiratory rate
- Mental status
- Systolic blood pressure

**B**

### SOFA Variables

- $PaO_2/FiO_2$ ratio
- Glasgow Coma Scale score
- Mean arterial pressure
- Administration of vasopressors with type and dose rate of infusion
- Serum creatinine or urine output
- Bilirubin
- Platelet count

The baseline Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have pre-existing (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP refers to mean arterial pressure.

**Figure 13: Operationalization of Clinical Criteria Identifying Patients with Sepsis and Septic Shock**

Adapted from Singer M, et al. *JAMA.* 2016;315(8):801-810.[45]

## LIST OF ABBREVIATIONS

| | |
|---|---|
| **AHF** | Acute Heart Failure |
| **BOOP** | Bronchiolitis Obliterans Organizing Pneumonia |
| **CAP** | Community-acquired Pneumonia |
| **COPD** | Chronic Obstructive Pulmonary Disease |
| **CRP** | C-reactive Protein |
| **CT-mRNA** | Calcitonin-messenger Ribonucleic Acid |
| **ED** | Emergency Department |
| **FEV1** | Forced Expiratory Volume in 1 Second |
| **GOLD** | Global Initiative for Chronic Obstructive Lung Disease |
| **ICU** | Intensive Care Unit |
| **IFN** | Interferon |
| **IL** | Interleukin |
| **LPS** | Lipopolysaccharide |
| **MRSA** | Methicillin-Resistant *Staphyloccus Aureus* |
| **PCT** | Procalcitonin |
| **Pro-CT** | Prohormone of Calcitonin |
| **PSI** | Pneumonia Severity Index |
| **qSOFA** | quick Sequential [Sepsis-related] Organ Failure Assessment score |
| **SIRS** | Systemic Inflammatory Response Syndrome |
| **SOFA** | Sequential [Sepsis-related] Organ Failure Assessment score |
| **TNF** | Tumor Necrosis Factor |
| **VAP** | Ventilator-associated Pneumonia |



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bioMérieux, Inc. • 100 Rodolphe Street • Durham, NC 27712 • U.S.A.
Tel: (800) 682 2666 • Fax: (800) 968 9494
**www.biomerieux-usa.com**