BIOMÉRIEUX

PROCALCITONIN

for Patient Monitoring and Guidance of Antibiotic Therapy

PIONEERING DIAGNOSTICS

THE CONTENT OF THIS BOOKLET WAS KINDLY WRITTEN BY:

Professor Philipp SCHUETZ, MD, MPH

Head of Medicine, Kantonsspital Aarau, Professorship and faculty at the University of Basel, Kantonsspital Aarau, Tellstrasse H7, CH-5001 Aarau, Switzerland

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PREFACE

A better understanding of the practical use of biomarkers among patients with infections has contributed significantly to individualization of care and rational therapeutic plans. Importantly, procalcitonin (PCT), a host-derived biomarker for systemic infections has emerged as the most reliable biomarker for early risk assessment and monitoring of individual patients with systemic infections and sepsis [1]. For optimal use of PCT, however, understanding its kinetics and disease- and setting specific cut-offs is mandatory [2-4]. Continuous education regarding PCT based on the most recent studies is thus warranted.

This booklet is intended as a practical guide and provides clinicians with an overview of the potential usefulness and limitations of PCT for risk assessment of progression to severe sepsis and septic shock, assessing disease severity and prognosis, monitoring patients and guiding clinical decisions on antibiotic therapy. While the first version of this booklet was published in 2019, we felt it was now necessary to update its content to reflect the state-of-the-art knowledge about best use of PCT for managing patients in different clinical scenarios and including the most recent guideline recommendations.

Specifically, this booklet aims to give clinicians information on how the biomarker PCT can be used in different clinical situations.

- **CHAPTER 1:** This section discusses preclinical data on the regulation of PCT, the kinetics over time and different cut-offs according to clinical settings.
- **CHAPTER 2:** The prognostic properties of PCT are discussed for risk assessment of patients, with examples from clinical research studies.
- **CHAPTER 3:** The use of PCT for monitoring patients and for guiding antibiotic decisions in different types of infections and clinical settings is illustrated.
- **CHAPTER 4:** A Question & Answer section discusses some remaining issues which are important when using PCT.

Philipp SCHUETZ, MD, MPH

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

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INTRODUCTION

Antibiotic overuse and misuse continues to rise and significantly contributes to the increase in resistant microorganisms and the serious issue of *Clostridioides difficile* infections worldwide, with important consequences for patient morbidity and healthcare costs [5].

These issues call for more effective efforts to **reduce the unnecessary and prolonged use of antibiotics** in self-limiting non-bacterial and resolving bacterial infections [3,6]. To help achieve this aim, biomarkers are increasingly used in patients with possible or proven infections to complement clinical judgement and interpretation of other diagnostic and prognostic tests.

The two main purposes of such blood markers are to:

- **support early risk stratification** and thus provide prognostic information regarding the risk for mortality and other adverse outcomes
- **tailor antibiotic therapies** to individual patient needs ("antibiotic stewardship").

Today, the most widely used blood biomarker for the purpose of managing patients with infections is PCT. During serious bacterial infections, PCT blood levels rise within 4-6 hours and levels drop by about 50% daily when infection is controlled and the patient responds adequately to antibiotics [7].

Without a doubt, the addition of PCT has had a strong impact on the way we care for patients today. Based on the regulation and kinetics of PCT, many studies have documented **the clinical utility of PCT for specific clinical settings and infections.**

- **In patients presenting with possible sepsis,** PCT improves early risk assessment [8].
- **For patients with suspected or confirmed sepsis,** PCT aids in decision-making on antibiotic discontinuation [9].
- **For respiratory infections,** monitoring of PCT has improved the tailored use of antibiotics with a reduction in antibiotic exposure of 30-70% depending on the clinical setting [10].
- **Monitoring of PCT** in different types of respiratory infections has resulted in other improved outcomes, such as lower risk of antibiotic-associated side effects, shorter length of hospital stays, and lower overall costs due to antibiotic savings [10].
- **During the coronavirus disease 2019 (COVID-19) pandemic,** PCT has been shown to improve early triage decisions by predicting severe courses of disease and high risk of treatment failure [6].

Still, it is important to realize that PCT cannot be used as a stand-alone test and does not replace clinical intuition or thorough clinical evaluations of patients. PCT needs to be used within well-defined clinical protocols to most efficiently aid physicians in making rational clinical decisions in individual patients with sepsis and respiratory infections.

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 [1].

ABOUT PROCALCITONIN (PCT)

1 What is PCT and where is it produced?

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[11]. PCT shows an interesting kinetic profile[12].

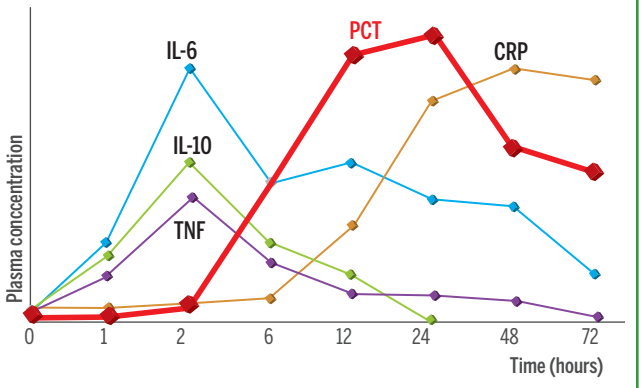
Cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF) show a fast initial spike upon infection, however, levels return to normal within a few hours. The high variability of these markers has been a major challenge for their use in clinical practice.

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**)[13]. **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 its course also has prognostic implications.

PCT has an interesting kinetic profile which allows monitoring of the individual patient's response to antimicrobial therapy.

Figure 1: Kinetic profiles of different biomarkers of bacterial infection.
Adapted with permission from Meisner M. *J Lab Med.* 1999;23:263-72[13].

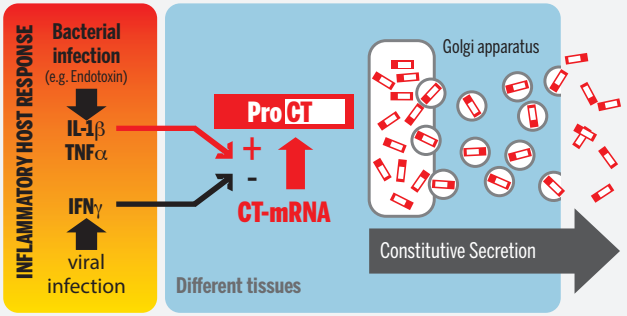


2 How is PCT regulated on a cellular level?

PCT production is induced in response to microbial toxins and to certain bacterial cytokines, particularly interleukin (IL)-1β, tumor-necrosis factor (TNF)-α and IL-6, and is released in the bloodstream where it can be measured (**Figure 2**)[14].

Conversely, PCT production is attenuated by certain cytokines released in response to a viral infection, particularly interferon-γ (IFN-γ). This selective cellular mechanism with different kinetic profiles in patients with viral and bacterial infections **makes PCT a more useful biomarker for the assessment of patients with systemic infections** as compared to other inflammatory markers (e.g., CRP) that **increase irrespective of bacterial or viral infections or other inflammatory diseases**.

Figure 2: Schematic diagram of the regulation of CALC-I gene expression leading to PCT release in cells during septic conditions.
Adapted with permission from Christ-Crain M *et al. Swiss Medical Weekly* 2005;135 (31-32):451-460 [14]. Creative Commons Licence BY-NC-ND 4.0



Pro-CT: Prohormone of calcitonin. CT-mRNA: Calcitonin-messenger ribonucleic acid

Early evidence indicated that PCT shows different kinetic profiles in patients with bacterial infections compared to those with viral infections or inflammatory conditions.

This makes PCT clinically more useful compared to other inflammatory markers, such as CRP.

3 Different PCT cut-offs in different clinical settings

For optimal use of PCT, levels should be put into the context of the clinical assessment regarding severity of illness and the probability that a patient has a serious bacterial infection (e.g., including results of other diagnostic tests, such as blood cultures or molecular polymerase chain reaction (PCR) tests). Yet, for an individual patient, the probability of the presence of a severe bacterial infection correlates with increasing levels of circulating PCT:

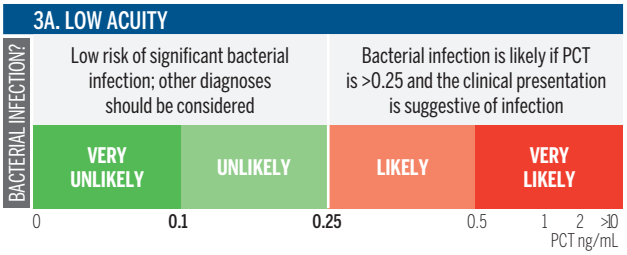
- **the higher the PCT level** in a patient with probable infection, the higher the probability of bacterial sepsis with severe outcome,
- **the lower the PCT level**, the lower the risk for a serious bacterial infection and the higher the probability that these patients may rather have mild self-limiting viral infections or other inflammatory diseases.

For optimal use, PCT cut-off values should be adapted to patient acuity (risk level), the probability that a patient has a bacterial infection and the clinical setting [4,15]

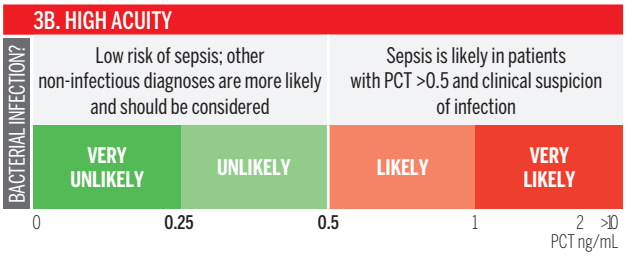
- In **low-acuity patients and/or patients with low risk for bacterial infections** (Figure 3A) [4], typically patients with respiratory tract infections presenting to their primary care physician or the emergency department (ED), a PCT cut–off of 0.25 ng/mL or 0.1 ng/mL has a very high negative predictive value to exclude a serious bacterial infection. Viral infections, such as bronchitis or viral-induced exacerbation of Chronic Obstructive Pulmonary Disease (COPD) are much more likely.
- In **high-acuity patients and/or patients with high risk for bacterial infections** (Figure 3B) [4], typically patients transferred to the intensive care unit (ICU), PCT cut–offs of 0.5 ng/mL or 0.25 ng/mL should be used. PCT levels below these cut-offs make severe bacterial infections and sepsis unlikely and other diagnoses explaining the patients' medical condition should be considered.

Figure 3: PCT cut-off levels adapted to acuity.
Adapted from Schuetz P *et al. BMC Medicine* 2011;9:107 [15] and Albrich WC *et al. Arch Intern Med.* 2012;172(9):715-722 [54].

LOW ACUITY refers to patients typically seen in primary care or the ED without clinical signs of severe infection / sepsis.



HIGH ACUITY refers to patients transferred to the intensive care unit because of severe disease.



USE OF PCT AS A PROGNOSTIC MARKER FOR PATIENT MONITORING

1 Kinetics of PCT in different types of viral and bacterial infections

PCT is mainly **up-regulated in response to severe bacterial infections and the drop of PCT correlates with resolution of infection**. In respiratory infections, PCT remains low (in the range of healthy subjects) in patients with the clinical diagnosis of self-limiting bronchitis – which is mostly a viral infection. Yet, it significantly increases in patients with bacterial pneumonia and has highest levels in patient with sepsis due to bacterial pneumonia[16].

Therefore, within the context of the overall clinical assessment in regard to severity of illness and the probability that a patient has a bacterial infection (e.g., including results of other diagnostic test such as blood cultures or PCR tests), **an initial PCT level can influence the therapeutic approach** to a patient with clinical signs of a respiratory infection[17,18].

Traditional culture methods, such as blood cultures, focus on identification and characterization of pathogens. This is important to know 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 microorganism and the severity of infection. PCT, on the other hand, mirrors the patient's response to the infection and therefore indirectly the extent and severity of infection. With new microbiological methods becoming available that rapidly identify microorganisms with higher sensitivity, **PCT may help to increase the specificity** of these methods by providing information about the severity and "relevance" of microbial culture results in individual patients.

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[19].

PCT is helpful for the correct interpretation of microbiological test results as it is up-regulated in response to severe bacterial infections.

PCT also provides additional information about the host response to the infection.

PCT also helps to accurately **predict the risk for bacteremic infection defined by blood culture positivity**. A retrospective study found PCT in combination with clinical signs to be a strong predictor for blood culture positivity among patients with different types of infections[20]. However, PCT may not help to reliably predict the type of bacterial microorganism. 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)[21].

PCT is not a substitute for microbiological tests. It does not identify microorganism 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 infection, as with increasing PCT concentrations, a serious bacterial infection becomes more likely. Conversely, an alternative diagnosis becomes more likely if PCT levels remain low.

2 PCT in patients presenting with possible sepsis

Sepsis affects an estimated 49 million people worldwide each year, including more than 20 million children under age 5, and nearly 5 million older children and adolescents (ages 5-19). Sepsis takes 11 million lives around the world each year, contributing to 20% of all deaths globally[22].

The cornerstone of today's sepsis treatment is **early recognition of the condition and early initiation of appropriate treatment**, including antibiotics, fluids and other treatments according to the specific circumstances. Clinical signs, such as the systemic inflammatory response syndrome (SIRS) criteria, lack both sensitivity and specificity. Therefore, it is important to **combine the clinical assessment with different diagnostic tests** (e.g. blood culture and PCR tests) **and host-response markers such as PCT**, that mirror the severity of infections[7,23].

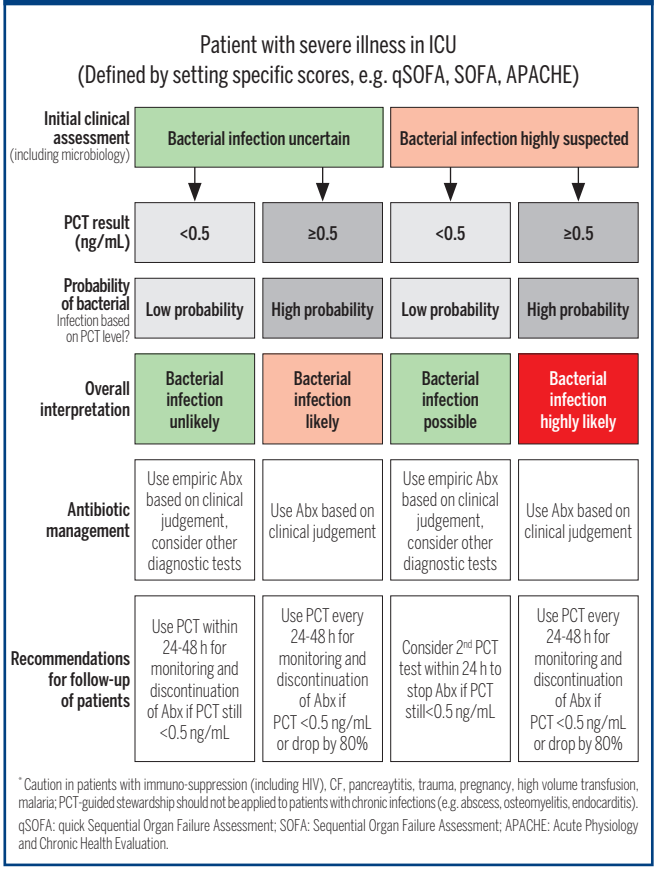
PCT has been demonstrated to be most clinically useful, and superior to commonly used clinical variables and laboratory tests in the **early assessment of patients with possible sepsis**[7]. PCT has been shown to correlate with the extent and severity of microbial invasion and **thus improves the clinical work-up of patients with suspicion of sepsis**[23].

- **In the ED setting**, low PCT values (<0.25 ng/mL) in patients with clinical signs of infection indicate a low probability for blood culture proof of bacterial infection and sepsis[24]. Usually PCT levels are found to be >0.5 ng/mL or higher if patients have bacterial infections leading to sepsis.
- **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 makes sepsis very unlikely (high negative predictive value) (Figure 4)[23,26].

PCT therefore **adds significant information for the differentiation between various clinical conditions mimicking severe systemic bacterial infections and sepsis**. New definitions of sepsis were published in 2016 and updated in 2021, which abandoned the notion of systemic inflammatory respiratory syndrome (SIRS) and considered the term severe sepsis to be redundant[25].

USE OF PCT AS A PROGNOSTIC MARKER FOR PATIENT MONITORING

Figure 4. Use of PCT in patients with severe illness in the ICU.
Adapted with permission from Schuetz P, *et al. Clin Chem Lab Med.* 2019;57(9):1308-1318[26]. Creative Commons Licence BY-NC-ND 4.0



* Caution in patients with immuno-suppression (including HIV), CF, pancreaytitis, trauma, pregnancy, high volume transfusion, malaria; PCT-guided stewardship should not be applied to patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis).

qSOFA: quick Sequential Organ Failure Assessment; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation.

PCT contributes significantly to the assessment of patients with possible sepsis:

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

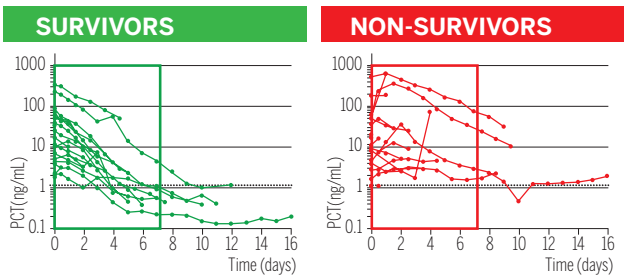
3 Prognostic value of PCT in the ED and ICU

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 **favourable patient outcomes**.

The following interpretation of PCT results based on clinical evidence has been suggested[27]:

- **in low-acuity patients with respiratory infections:**
  a) a **low PCT level** identifies patients at lower risk for a bacterial etiology and community-acquired pneumonia (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 5**)[23,28]. Levels failing to decline during initial follow-up identify patients not responding to therapy. This latter conclusion is also in accordance with ICU studies focusing on sepsis patients and ventilator-associated pneumonia (VAP) patients demonstrating that a **decreasing PCT level over time is a more sensitive outcome predictor** than the initial PCT level[23,28].

Figure 5: Daily variations of PCT levels during ICU hospitalization in patients admitted with sepsis and septic shock that survived or did not survive.
Adapted with permission from Harbarth S, *et al. Am J Respir Crit Care Med.* 2001;164: 396-402 and Schuetz P, *et al. Crit Care.* 2013;17(3):R115[23,28].

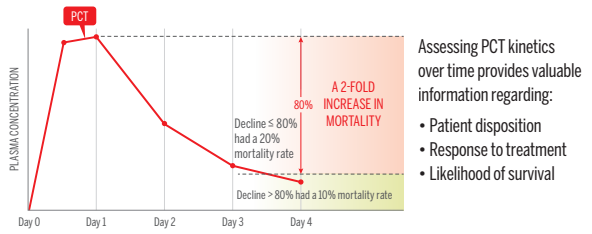


The Procalcitonin MOnitoring SEpsis Study (MOSES) has helped expand the clinical utility of PCT[8,28]. In this study, PCT is used to help assess the response of septic patients to treatment by comparing a baseline PCT measurement with a PCT value taken on day four. **Monitoring the change in PCT over 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 (**Figure 6**).

The key findings of this major multi-site U.S. 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 2-fold increased risk of death was observed (20% mortality rate), compared to those who experienced a decrease in PCT > 80% (10% mortality rate).
- 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.

Figure 6. Using PCT kinetics to assess mortality risk over time.
Adapted from Schuetz P, *et al. Crit Care Med.* 2017;45(5):781-789[8] and Schuetz P, *et al. Crit Care.* 2013;17(3):R115[28].



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

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

4 Use of PCT in pediatrics

PCT is a very useful biomarker in pediatric populations. The NeoPIns study found that PCT-guided decision-making significantly shortened the duration of antibiotic therapy in newborns with suspected early onset sepsis, and the ProPAED study showed that PCT-guided therapy significantly reduced antibiotic exposure in children and adolescents with lower respiratory tract infection (LRTI)[29,30].

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

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)[30]. This effect was most pronounced in pneumonia patients (9.1 days in PCT group vs 5.7 days in control patients).

In a European randomized trial on antibiotic use in neonates, the use of a PCT cut-off of 0.25 ng/mL to rule out the need for initiation or continuation of antibiotics significantly reduced antibiotic exposure in children by almost 50% without apparent harmful effects[29].

ASSESSMENT OF CHILDREN WITH MENINGITIS

A PCT level ≥ 0.5 ng/mL associated with a high CSF protein level and interpreted with clinical rules is a sensitive and specific marker to identify severe bacterial meningitis. Using PCT in the assessment of **children with possible meningitis** improves the correct therapeutic management and thereby reduces length of hospital stay in children with viral meningitis[31].

ASSESSMENT OF CHILDREN WITH FEBRILE URINARY TRACT INFECTIONS

PCT can help in the work-up of children with acute pyelonephritis and prediction of renal scars, as a PCT level ≥ 0.5 ng/mL has been associated with higher probability for renal damage and renal scars. A PCT value ≥ 0.5 ng/mL has also been associated with high-grade (≥ 3) vesico-ureteral reflux (VUR)[32].

ASSESSMENT OF SEVERE BACTERIAL INFECTIONS IN CHILDREN ≥ 3 MONTHS OF AGE WITH FEVER WITHOUT SOURCE

In children >3 months of age presenting with fever without source (FWS), a PCT cut-off of 0.5 ng/mL has been associated with severe bacterial infection (SBI), while lower levels have been associated with non-severe or viral infections. Combining PCT with other biomarkers of inflammation in the "Lab-score" was also found to be most useful in predicting SBI[33].

ASSESSMENT OF CHILDREN WITH POSSIBLE PNEUMOCOCCAL PNEUMONIA

Elevated PCT and CRP in combination with a positive pneumococcal urinary antigen have been proven to reliably predict pneumococcal pneumonia[34].

USE OF PCT AS A PROGNOSTIC MARKER FOR PATIENT MONITORING

NEONATES

Similar to adult patients, normal PCT values in infants are <0.05 ng/mL. In neonates, however, PCT levels are physiologically increased without an infection being present and vary depending on hours of age during the first two days of life (**Table 1**)[35]. This increase may mirror the physiological processes in the gut that take place in early life.

Table 1: PCT levels in neonates
Adapted from Chiesa *et al. Clin Chim Acta*. 2011;412 (11-12):1053-9[35].

AGE (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

Serum PCT levels at presentation have been shown to accurately predict severe neonatal sepsis with an area under the curve (AUC) of 0.87[36]. In a large prospective study on neonates, **PCT was shown to be the best marker for identifying bacteremia and bacterial meningitis in febrile infants 7 days to 3 months old**[37].

Several randomized intervention studies have shown that the use of a PCT-guided protocol can **shorten antibiotic therapy in suspected neonatal early-onset sepsis**[38]. Most importantly, the multi-center NeoPIns study involving over 1,700 neonates demonstrated that, compared to standard care, a PCT-guided protocol significantly reduces the duration of antibiotic therapy (55 h vs 65 h)[29].

Elevated umbilical **blood cord PCT concentration** has been described as an independent risk factor of mortality in preterm infants[39]. Lencot *et al.* evaluated the diagnostic value of an umbilical blood cord PCT based protocol in newborns suspected of early onset neonatal infections (EONI)[40].

This protocol allowed a significant decrease in the number of blood tests and antibiotic prescriptions, and proved to be a safe alternative compared to current standard of care. This study shows PCT to be a new and efficient marker to guide neonatologists taking care of newborns suspected of EONI, however these results need confirmation in future trials.

In the pediatric setting, PCT contributes to early prognosis and therapeutic management and allows antibiotic guidance.

It can help to avoid unnecessary hospitalization and antibiotic exposure in children with viral meningitis or low risk of bacterial infection.

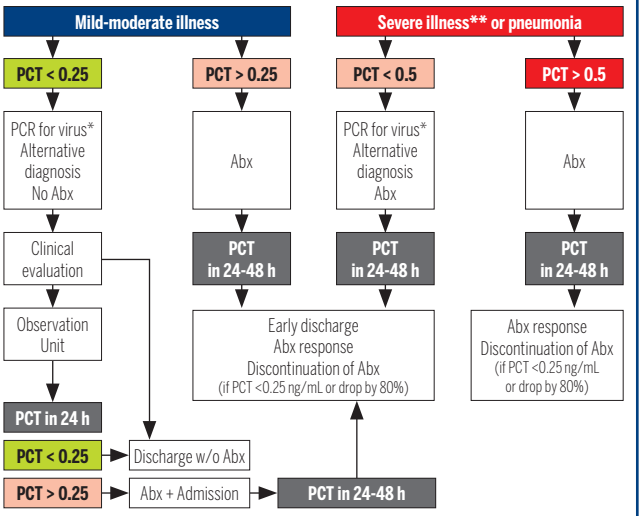
5 Use of PCT in geriatrics

Optimal treatment of infections in elderly patients is particularly challenging because clinical symptoms and signs are often less specific, resulting in both over- and under-treatment. This group of patients is also particularly vulnerable for side-effects from antibiotic treatment, and limiting the use of antibiotics is therefore highly important. Elderly patients have been shown to display a less pronounced immune response to infection, which may influence the kinetics of different host-derived biomarkers of infection.

There is currently strong evidence that **PCT is helpful for risk stratification and for guiding individual treatment decisions in the elderly** and PCT is thus of particular interest in the geriatric patient population [41]. Specifically, in a meta-analysis based on individual patient data focusing on elderly patients including individual patient data from 9,421 participants from 28 randomized trials from around the world, use of PCT was found to result in significant reductions in antibiotic exposure due to shorter antibiotic treatment durations [42]. At the same time, use of PCT was found to significantly reduce mortality in PCT-guided patients compared to control group patients due to different effects, including better monitoring of patients and lower risk for antibiotic side effects. These data also support the use of PCT in the very old patient as an effective means to lowering antibiotic exposure with no apparent harmful effects.

Based on the results of previous trials, a **consensus algorithm has recently been proposed for PCT use in combination with clinical scores for clinical decision-making** (Figure 7) [41]. The algorithm stratifies patients on severity of illness and different PCT cut-offs, and recommends use of antibiotics for patients with high probability and high PCT levels. For patients with low probability and low PCT levels, it is recommended to search for alternative diagnoses.

Figure 7: Proposed PCT algorithm for use in elderly patients with mild, moderate or severe respiratory infection.
Adapted from Falcone M *et al. Aging Clin Exp Res.* 2023:1-11 [41]. Open Access CC-BY 4.0



* Non Abx if a virus identified and PCT <0.5
** National Early Warning Score (NEWS) of ≥5 or quick Sequential Organ Failure Assessment (qSOFA) ≥2

The elderly represent a particularly vulnerable patient population where clinical signs and symptoms of infection are often ambiguous, resulting in high risk for both under- and over-treatment.

Although the host-response may be less pronounced in the elderly, use of PCT algorithms has been shown to improve risk stratification and antibiotic management of geriatric patients.

6 Use of PCT in patients with COVID-19

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has dramatically shown the importance of effectively managing infections to improve management and survival of patients worldwide. COVID-19 symptoms range from undetectable to deadly, but most commonly include fever, dry cough, and fatigue. Complications may include pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, septic shock, and death.

To optimally use hospital resources and treat the patients at high risk for complications, there has been much interest in using biomarkers, including PCT. Patients with COVID-19 often present with unspecific symptoms, which are also common in other respiratory diseases, making differentiation from bacterial infection challenging. In this respect, PCT can be of help regarding the prognostic and therapeutic management [6].

Numerous studies have reported that **PCT levels correlate significantly with the severity of COVID-19, including risks for complications and mortality** [6]. PCT has thus been included in several prognostic risk scores for assessing patients in the emergency department [43].

Studies have shown that PCT levels (>0.5 ng/mL) indicate hyperinflammation and high risk for the cytokine storm typically seen in severe COVID-19 progression. **Identification of patients at risk for disease progression may help to initiate anti-inflammatory medication** (e.g. corticosteroids) early, thus reducing viral load and avoiding hyper-activation of the immune system. In addition, studies also reported higher PCT levels in severe COVID-19 patients with disseminated intravascular coagulation (DIC) and in patients with bacterial coinfection [44]. The therapeutic consequences of elevated PCT levels should thus not only focus on antibiotic administration but also on other treatment requirements.

PCT has been shown to improve the clinical assessment of patients with COVID-19 by providing prognostic information on disease severity, risk of complications and risk for hyperinflammation, a condition that can be treated with anti-inflammatory treatments [6].

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 to preserve their efficacy. More efforts are required to **reduce the unnecessary and prolonged use of antibiotics** in self-limiting non-bacterial and resolving bacterial infections.

It has been shown that PCT can be used in different clinical settings to help **guide decisions to start, continue or stop antibiotic therapy** based on initial PCT levels and repeated measurements, thereby contributing to **efficient antibiotic stewardship** [4,45].

1 Guideline recommendations

SURVIVING SEPSIS GUIDELINES

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [25]. Sepsis and septic shock are major healthcare problems, impacting millions of people around the world each year. Early identification and appropriate management in the initial hours after the development of sepsis improve outcomes – particularly if shock is present (Figure 8).

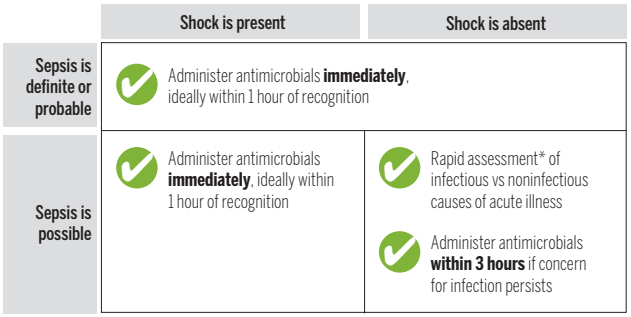
In order to optimize and standardize treatment of sepsis, the Surviving Sepsis Campaign (SSC) regularly issues and updates international guidelines for Management of Sepsis and Septic Shock with a recent update in 2021 [25]. These guidelines also focus on the recommended use of PCT regarding antibiotic management of the septic patient with **two specific recommendations regarding admission PCT levels and monitoring of patients with PCT**.

- **Firstly**, the panel issued a weak recommendation against using a single PCT level on admission to guide antimicrobial initiation in patients with sepsis or septic shock. In a **very high risk situation with high probability of bacterial infection, the focus should be on immediate treatment**.

- **Secondly**, however, the guidelines recommend that **PCT should be used in conjunction with clinical evaluation to decide when to discontinue antimicrobials** because this strategy has been shown to be effective in improving treatment and clinical outcomes in several trials.

Thus, initial start of antimicrobial treatment based on clinical grounds only and later de-escalation based both on clinical assessment and PCT is the recommended approach in the high-risk patient population [9].

Figure 8: Recommendations on timing of antibiotic administration.
Adapted with permission from Evans L *et al. Crit Care Med.* 2021, 49(11):e1063-e1143 [25].



* Rapid assessment includes history and clinical examination, tests for both infectious and non-infectious causes of acute illness and immediate treatment for acute conditions that can mimic sepsis. Whenever possible this should be completed within 3 hours of presentation so that a decision can be made as to the likelihood of an infectious cause of the patient's presentation and timely antimicrobial therapy provided if the likelihood is thought to be high.

Currently, sepsis guidelines recommend:

- **against use of PCT to decide for or against antibiotic treatment in patients presenting with sepsis or septic shock;**
- **for use of PCT to decide when to stop antibiotics in a septic patient showing clinical signs of improvement.**

Recommendations of the 2021 SSC guidelines [25]:

Recommendation 16. For adults with suspected sepsis or septic shock, we suggest against using PCT plus clinical evaluation to decide when to start antimicrobials, as compared to clinical evaluation alone.
(Weak recommendation, very low quality of evidence)

Recommendation 31. For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we suggest using PCT AND clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone.
(Weak recommendation, low quality of evidence)

AACC GUIDELINES

In 2023, the American Association for Clinical Chemistry (AACC) issued guidelines on the use of PCT [46]. They concluded that overall, the evidence to support the **use of PCT to guide antibiotic cessation is compelling in the critically ill and in LRTIs** but is lacking in other clinical scenarios, and is limited in pediatric and neonatal populations. Interpretation of PCT results requires guidance from multidisciplinary care teams of clinicians, pharmacists, and clinical laboratorians. They also concluded that **PCT testing should be incorporated into broad antimicrobial stewardship efforts** that draw on the expertise of multidisciplinary teams.

ERS/ESICM/ESCMID/ALAT GUIDELINES FOR THE MANAGEMENT OF SEVERE COMMUNITY-ACQUIRED PNEUMONIA

In 2023, several societies including the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Latin American Thoracic Association (ALAT) issued guidelines for the management of severe CAP including use of PCT [47].

The guideline recommends **use of PCT to reduce the duration of antibiotic treatment in patients with severe pneumonia**. However, the guideline also points out that this recommendation must be considered together with **clinical assessment with the aim of reducing antibiotic treatment duration**. PCT might not be useful when clinical stability is achieved, and duration of antibiotic therapy is between 5 and 7 days.

OTHER INTERNATIONAL GUIDELINES

Several other international guidelines from different countries, societies and clinical settings exist and provide guidance on the use of PCT [3,26,48]. While these guidelines may differ in several aspects and in the grade of recommendation based on trial data for the specific patient population in question, there are some overall concepts where experts worldwide agree.

- **Firstly,** most guidelines reemphasize that **PCT should be put into the context of the clinical assessment regarding severity of illness and probability of bacterial infection**, in order to make reasonable recommendations. PCT should thus not be viewed as a standalone test, but as an adjunct to clinical evaluation of the patient. PCT algorithms should thus differ based on severity of illness and probability of bacterial infection (based on clinical grounds and results of other microbiological tests).

While in patients with mild disease and low probability of bacterial infection, a low PCT level may advise physicians for or against the use of antibiotic treatment, for patients with moderate or high severity, empiric therapy is a priority regardless of the PCT result. In such a situation, retesting of PCT after 6–24 h may support patient monitoring and early de-escalation of therapy.

- **Secondly**, most guidelines also mention that the majority of data today has been generated for respiratory tract infections and sepsis. There is thus a need for additional studies and trials to **investigate the best use of PCT in other infections and also in settings with other types of pathogens** (e.g. patients with tropical diseases)[3]. Finally, guidelines also recommend **continuous education of healthcare professionals** for optimal use of PCT in clinical routine.

Several guidelines have been issued with recommendations regarding the best use of PCT across different diseases and settings.

Overall, experts agree that PCT levels need to be evaluated within the clinical patient context after a thorough clinical assessment considering severity of illness and probability of bacterial infection, in order to make reasonable recommendations.

2 Use of PCT in Primary Care

Differentiation between viral and bacterial origin of infection in low-acuity patients presenting with symptoms of upper and lower respiratory tract infections (URTI/LRTI) in the primary care outpatient setting remains a difficult task.

A PCT strategy for guiding antibiotic therapy in URTI/LRTI has two different effects:

- improving the diagnostic ability of the physician to rule out or confirm bacterial infections,
- reassuring patients that antibiotics are not necessary.

A meta-analysis which served as the basis for a 2017 Cochrane Systematic Review investigated the effect of using PCT to initiate or discontinue antibiotics in patients with acute respiratory infections (ARIs)[10]. It demonstrated that **PCT-guided treatment significantly improved clinical outcomes in patients with ARIs from different clinical settings** (Table 2)[49].

- **Mortality at 30 days** was significantly lower in PCT-guided patients than in control patients (9% vs. 10%, p = 0.037). This mortality benefit was consistent across clinical settings and among different types of infections, with the exception of primary care settings and patients with bronchitis where mortality was extremely low.
- **Total antibiotic exposure** was significantly lower in the PCT-guided patients than control patients (5.7 days vs. 8.1 days, p = <0.0001) and was attributable to lower initial prescription rates (primary care setting), lower prescription rates and shorter therapy duration (ED), and shorter treatment durations (ICU).
- **Antibiotic-related side-effects** were significantly reduced in PCT-guided patients compared to control patients (16% vs. 22%, p = <0.0001)

Table 2: Effect of using PCT to initiate or discontinue antibiotics in patients with acute respiratory infections
Adapted from Schuetz P. *et al. Lancet Infect Dis.* 2018;18(1):95-107[49]

	PCT group (n=3336)	Control (n = 3372)	p-value
30 day mortality	286 (9%)	336 (10%)	0.037
Total antibiotic exposure, days (*mean*)	5.7	8.1	<0.0001
Antibiotic-related side effects	16%	22%	<0.0001

In patients with acute respiratory infections, PCT-guided treatment is associated with a decreased risk of mortality, lower treatment failure rate, reduced antibiotic exposure and fewer antibiotic-related side effects.

3 Use of PCT–guided antibiotic therapy in LRTI in the ED and outpatients

LRTIs such as CAP, bronchitis or exacerbation of COPD are most often viral infections. Nevertheless, patients are still often being over-treated with antibiotics, because it is difficult to rule out a bacterial etiology based on clinical grounds. Several studies have investigated the role of PCT in addition to clinical judgement and radiological tests (e.g. lung ultrasound)[50].

Also, a 2023 US based study that enrolled 499 patients from outpatient clinics and emergency departments found low PCT levels can be used to identify adults with LRTIs who are unlikely to benefit from antibiotic therapy[51].

BRONCHITIS AND COPD EXACERBATION

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 over a pre-determined threshold (>0.25 ng/mL)**.

- 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 re-measurement of PCT is recommended (**Figure 10**).

This concept has been investigated in different trials including more than 1,000 patients with bronchitis and COPD exacerbation[45]. 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.

- **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.**

COMMUNITY-ACQUIRED PNEUMONIA

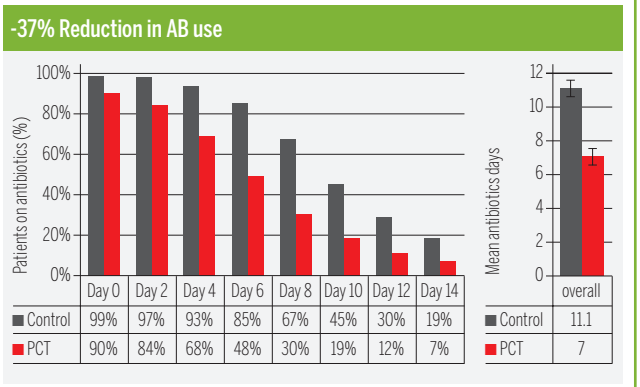
The greatest amount of clinical evidence for using PCT for antibiotic decisions is derived from randomized antibiotic stewardship trials involving over 2,000 patients with CAP[10,45,52].

Based on these trials, **a PCT level >0.25 ng/mL** strongly suggests that a **bacterial infection is likely** and **antibiotic therapy should be rapidly initiated**. If PCT testing is available with 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. In 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 by at least 80-90% from the peak level)**.

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 9**).

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.

Figure 9: Antibiotic use in CAP patients with (red) and without (grey) PCT guidance.
Adapted from Schuetz P, *et al. Cochrane Database Syst Rev.* 2017;10(10):CD007498[10]; Schuetz P, *et al.* Clin Infect Dis. 2012;55(5):651-62[45]; Schuetz P, *et al. Lancet Infect Dis.* 2018;18(2):141[52].



	Day 0	Day 2	Day 4	Day 6	Day 8	Day 10	Day 12	Day 14
Control	99%	97%	93%	85%	67%	45%	30%	19%
PCT	90%	84%	68%	48%	30%	19%	12%	7%

	overall
Control	11.1
PCT	7

With PCT guidance, patients with CAP 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% (Figure 9).

In patients suspected of having a pneumonia based on the presence of infiltrates, a consistent PCT level over 24-48 hours of <0.10 ng/mL or even 0.10 ng/mL to <0.25 ng/mL argues against a typical bacterial infection. Physicians should then consider including 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[45,53].

PCT-GUIDED ANTIBIOTIC THERAPY PROTOCOL

The ProREAL Study investigated the "real-life" effects of PCT-guided antibiotic therapy in a large international multicenter surveillance trial, which enrolled 1,820 patients presenting with LRTIs in the Emergency Department and physician offices, of which 1,520 had a final diagnosis of LRTI[54]. The study demonstrated that following a PCT protocol significantly reduces antibiotic use without increasing the risk of complications in real-life conditions, and showed a significant reduction of 1.51 days in antibiotic exposure in the PCT guided arm vs. standard therapy without increasing the risk of complications (Figure 10).

The ProREAL study demonstrates that following a PCT protocol significantly reduces antibiotic use without increasing the risk of complications in 'real-life' conditions[54].

Good compliance with the PCT protocol is possible in 'real-life' conditions but depends on antibiotic-prescribing cultures and may need to be reinforced to achieve optimal benefit.

USING PCT TO GUIDE ANTIBIOTIC THERAPY DECISIONS

Figure 10: Protocol for procalcitonin (PCT)-guided antibiotic therapy in patients with suspected or confirmed LRTI.
Adapted by permission from JAMA Internal Medicine. Albrich WC, *et al. Arch Intern Med.* 2012;172(9):715-722[54].

PCT result (ng/mL)	<0.10	0.10 - 0.25	0.26 - 0.50	>0.50
Recommendation regarding use of Abx	STRONGLY DISCOURAGED	DISCOURAGED	RECOMMENDED	STRONGLY RECOMMENDED

FOLLOW-UP IF NO ANTIBIOTIC THERAPY IS INITIATED:

- Repeat PCT measurement within 6-24 h (also in outpatients if symptoms persist/worsen)
- Differential diagnosis? e.g, pulmonary embolism, congestive heart failure, tumor, BOOP, viral, fungal

Antibiotic therapy can be considered for:

1. **Admission to the ICU or IMC**: (a) respiratory instability (respiratory rate ≥30/min or O2 saturation <90% with 6 L O2/min); (b) hemodynamic instability (systolic blood pressure for at least 1 h <90 mm Hg, despite adequate volume replacement or need for vasopressors)
2. **Life-threatening comorbidity**: (a) imminent death; (b) severe immunosuppression (neutrophils <500/µL; for HIV: CD4 <350/µL); (c) chronic infection or other non-respiratory infection requiring antibiotics (eg, endocarditis, TB)
3. **Complications and difficult-to-treat-organisms**: Legionella (antibiotics ≥10 d), abscess, empyema
4. **(a) PCT <0.10 ng/mL**: CAP PSI V (>130) or CURB-65 >3 points, COPD GOLD IV;
   (b) PCT 0.10-0.25 ng/mL: CAP PSI IV and V (>90), CURB-65 >2, COPD GOLD stages III and IV, SaO2 <90% despite 30 minutes of intensive oxygen therapy.

Falsely low PCT: eg, parapneumonic effusion, loculated infection (empyema), early phase of infection, fungal, most severe immunosuppression

FOLLOW-UP IF ANTIBIOTIC THERAPY IS INITIATED:

Follow-up if antibiotic therapy is initiated:

- **Check PCT on control days 2-3, 4-5, 6-8, and every 2 days after day 8 for guidance of antibiotic therapy**
- **To stop ongoing antibiotic therapy, use the same cutoff values as above**
- **For outpatients, duration of antibiotic therapy depends on last PCT value**: (≥0.25 ng/mL 3 d, ≥0.50 ng/mL 5 d, ≥1.0 ng/mL 7 d)
- **For initially very high PCT (e.g. >5 ng/mL), follow the relative decline of PCT if patients show clinical improvement** :
  - Decline ≥80% of peak: stop recommended
  - Decline ≥90% of peak: stop strongly recommended
- **Persistently elevated PCT**: suspect complicated course (resistant organism, MOF, abscess...)
- **Falsely elevated PCT**: eg, severe SIRS and shock, ARDS, trauma, postoperative, tumor (eg, medullary thyroid cancer, SCLC), fungal, malaria

ARDS, acute respiratory distress syndrome; BOOP, bronchiolitis obliterans with organizing pneumonia; CAP, community-acquired pneumonia; COPD GOLD, chronic obstructive pulmonary disease Global Initiative for Chronic Obstructive Lung Disease; CURB-65, confusion, serum urea nitrogen, respiratory rate, blood pressure, and age 65 years or older; HIV, human immunodeficiency virus; ICU, intensive care unit; IMC, intermediate care unit; MOF, multiple organ failure; PSI, Pneumonia Severity Index; SCLC, small-cell lung cancer; SIRS, sepsis inflammatory response syndrome; TB, tuberculosis

BENEFITS OF COMBINING PCT WITH OTHER PATHOGEN-DIRECTED DIAGNOSTICS

Several studies have suggested that **combining host-derived biomarkers, such as PCT, with pathogen-specific diagnostics, such as multiplex PCR, further improves the diagnostic management of patients** [55,56]. Such a strategy has resulted in a significantly higher proportion of antibiotic discontinuation or de-escalation in ED patients with proven viral infection [55]. Furthermore, neuraminidase inhibitor uses increased, and duration of intravenous antibiotics was significantly shortened.

4 Use of PCT in Critical Care

SEPSIS IN THE ICU

The **Stop Antibiotics on PCT guidance Study (SAPS)** published in 2016 is the largest randomized interventional multicentre trial conducted so far to assess the utility of PCT for antibiotic stewardship in critically ill adults [57].

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.

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.

A 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 [58]. It found that a **PCT level ≥2.0 ng/mL is most sensitive and specific for sepsis** and a **PCT level <0.50 ng/mL is safe to stop antibiotics in septic ICU patients**.

The review [58] also supports the use of PCT-based protocols, such as those recommended by Schuetz *et al.* (**Figure 11**) [4].

- A patient with a **systemic inflammatory response and an initial PCT level <0.50 ng/mL** is very unlikely to have an infectious etiology of the SIRS response, and **antibiotics can be stopped earlier**. 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 above 2 ng/mL** are diagnostic of sepsis with a high specificity and high Positive Predictive Value (PPV), and **antibiotic therapy should be started immediately**.
  Careful clinical evaluation and periodic monitoring (every 1- 2 days) of PCT levels after antibiotic initiation is an appropriate strategy in these patients [4].

- A drop of PCT to <0.50 ng/mL (or by at least 80-90% from peak values) appears to be an acceptable and safe threshold for **stopping antibiotic therapy**, assuming patients also show a favorable clinical response [4].
- **If PCT levels do not decrease by about 50% every 1-2 days, treatment failure should be considered** and patient re-assessment is recommended [4].

The use of PCT to decide when to **stop antibiotics based upon a level < 0.50 ng/mL** in patients with pulmonary infections and/or sepsis has been shown to **reduce total antibiotic usage and decrease the duration of antibiotics**. [58]

In clinical studies 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 [3,26,45].

Figure 11: Proposed protocol for use of PCT values to determine antibiotic treatment in HIGH-ACUITY INFECTIONS (ie, high risk; sepsis) in intensive care unit settings.
Adapted with permission from JAMA Internal Medicine. Schuetz P, *et al. Arch Intern Med.* 2011;171(15):1322-1331 [4].

Evaluation at time of admission

PCT result (ng/mL)	<0.25	0.25 - <0.50	0.50- <1.0	≥1.0
Recommendation regarding use of Abx	STRONGLY DISCOURAGED	DISCOURAGED	ENCOURAGED	STRONGLY ENCOURAGED
Overruling the algorithm	Empirical therapy recommended in all patients with clinical suspicion of infection			
Follow-up/ other comments	Considerer alternative diagnosis; reassess patients condition and recheck PCT level every 2 days		Reassess patients' condition and recheck PCT level every 2 days to consider stopping Abx	

Follow-up evaluation every 1 to 2 days

PCT result (ng/mL)	<0.25 or drop by >90%	0.25 - <0.50 or drop by ≥80%	≥0.50 and drop by <80%	≥1.0 and PCT rise
Recommendation regarding use of Abx	STOPPING ABx STRONGLY ENCOURAGED	STOPPING ABx ENCOURAGED	CONTINUING ABx ENCOURAGED	CONTINUING ABx STRONGLY ENCOURAGED
Overruling the algorithm	Consider continuation of Abx if patients are clinically not stable			
Follow-up/ other comments	Clinical reevaluation as appropriate		Consider treatment to have failed if PCT level does not decrease adequately	

An initial 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.

COMMUNITY-ACQUIRED PNEUMONIA IN THE ICU

Antimicrobial overuse in ICU patients with viral 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).

PCT has been found to be a helpful marker in excluding influenza in ICU patients with pneumonia. A 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%)[53].

Moreover, in this study, **PCT was found to be more accurate than CRP**, which is still the standard biomarker routinely used in many ICUs.

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[59].

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[60].

- 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[61].

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 stratification**, 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 [62].

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

FREQUENTLY ASKED QUESTIONS

1 Is there an international standard for PCT assays?

Many PCT (PCT) assays exist in the market today. All B·R·A·H·M·S PCT™ assays meet the highest international quality standards, are calibrated on the same standard, and offer excellent correlation and concordance at the established clinical cut-offs[2]. In case of patient follow-up, it is recommended to use the same PCT assay technique.

2 What are the clinical limitations of PCT?

- **Elevated PCT levels** may be observed 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, **low PCT levels** may be 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.

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

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[7,8,11,35,54,72]. These include, but are not limited to:

- neonates < 48 hours of life (physiological elevation)
- 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
- invasive fungal infections or acute attacks of *Plasmodium falciparum*
- prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, small cell lung cancer, medullary C-cell carcinoma of the thyroid.

LOW PCT levels do not automatically exclude the presence of bacterial infection[54]

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.

3 What is the value of PCT in immunosuppressed patients?

Different studies have evaluated the utility of PCT in patients with febrile neutropenia and shown PCT to be of great value as a prognostic marker[63]. One randomized trial found PCT to be a strong predictor for bacteremia, but a PCT protocol did not significantly reduce antibiotic exposure in this setting[64]. Clearly, more interventional research is still required in the population of immune-suppressed patients.

Importantly, the production of PCT does not seem to be attenuated by corticosteroids and PCT production does not rely on white blood cells. A study comparing different biomarker kinetics in patients treated with 50 mg prednisone found that PCT was much more stable, while CRP and white blood cell count (WBC) were much more influenced by corticosteroids with CRP levels significantly dropping and WBC significantly increasing[65].

Observational studies in immunosuppressed patients demonstrated that PCT levels are not affected by corticosteroids.

4 Is PCT testing cost-effective?

An important consideration when using a new diagnostic test is the cost associated with the test with respect to the potential for producing other healthcare-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 [65-70].

An extensive retrospective US-database analysis of the clinical and cost impact of PCT testing 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 [69]. A recent prospective trial from Greece also reported cost-savings with use of PCT due to shorter length of stay and lower risks for infection-associated adverse events [66].

Likewise, a 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 [70]. 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.

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 Other applications

PCT AND FUNGAL INFECTIONS

Several studies have demonstrated the potential clinical utility of PCT in predicting invasive fungal infections [71,72]. PCT shows a high negative predictive value for detection of *Candida* spp. and could represent a useful diagnostic tool to exclude fungal infection in septic patients, limiting unnecessary use of antifungal treatments. However, this needs to be assessed in further larger interventional studies.

PCT IN HEMODIALYSIS PATIENTS

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 [73]. 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.

PCT AND ASTHMA

A clinical study from Long *et al.*, with 12 month follow-up, showed that a PCT-guided strategy allows antibiotic exposure to be reduced in patients with severe acute exacerbation of asthma without apparent harm [74]. Given the prevalence of asthma and the duration of illness, a reduction in antibiotic prescriptions in case of exacerbations could result in fewer side effects and lower treatment costs, as well as helping to reduce antimicrobial resistance, particularly in countries with an overuse of antibiotics. Additional larger multicenter studies are required to confirm these findings.

LIST OF ABBREVIATIONS

AACC	American Association for Clinical Chemistry
AHF	Acute heart failure
ALAT	Latin American Thoracic Association
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Acute respiratory distress syndrome
ARI	Acute respiratory infection
BOOP	Bronchiolitis obliterans organizing pneumonia
CAP	Community-acquired pneumonia
CARC	Community-acquired respiratory co-infection
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CT-mRNA	Calcitonin-messenger ribonucleic acid
DIC	Disseminated intravascular coagulation
ED	Emergency department
EONI	Early onset neonatal infection
ERS	European Respiratory Society
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESICM	European Society of Intensive Care Medicine
FEV1	Forced Expiratory Volume in 1 second
FWS	Fever without source
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICU	Intensive care unit
IFN	Interferon
IL	Interleukin
LPS	Lipopolysaccharide
LRTI	Lower respiratory tract infection
NEWS	National Early Warning Score
PCR	Polymerase chain reaction
PCT	Procalcitonin
Pro-CT	Prohormone of calcitonin
PSI	Pneumonia severity index
qSOFA	quick Sequential Organ Failure Assessment
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBI	Severe bacterial infection
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential Organ Failure Assessment
SSC	Surviving Sepsis Campaign
TNF	Tumor necrosis factor
VAP	Ventilator-associated pneumonia
WBC	white blood cell count

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NOTES

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bioMérieux S.A. • 69280 Marcy l'Étoile • France
Tel.: + 33 (0)4 78 87 20 00 • Fax: +33 (0)4 78 87 20 90
www.biomerieux.com