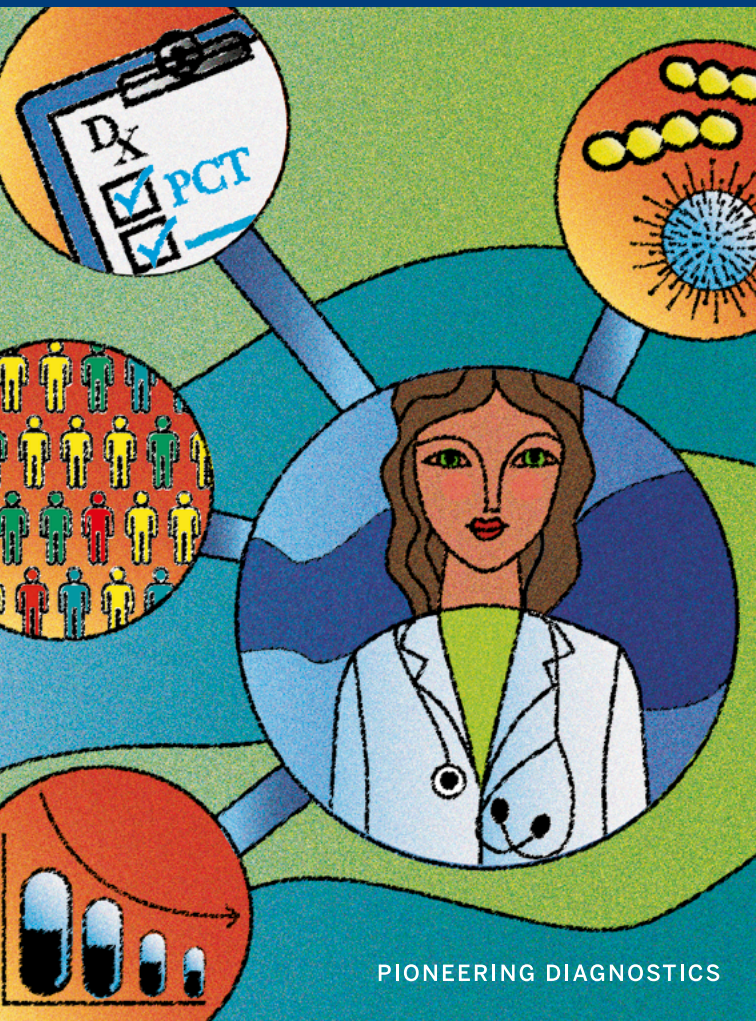
BIOMÉRIEUX

PROCALCITONIN

For diagnosis and guidance of antibiotic therapy



PIONEERING DIAGNOSTICS

THE CONTENT OF THIS BOOKLET WAS KINDLY WRITTEN BY:

Prof. Philipp SCHUETZ, MD, MPH
Senior Consultant, Medical University Department
Internal Medicine and Emergency Medicine
Kantonsspital Aarau, Tellstrasse H7, CH-5001 Aarau
Professorship and faculty at the University of Basel

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

WE ALSO WISH TO THANK:

Prof. Alain GERVAIX
Department of Pediatrics
Geneva University Hospitals (HUG),
Geneva, Switzerland

and

Dr Andreas HOHN
Department of Anaesthesiology, Intensive Care, Palliative Care and Pain Medicine, BG University Hospital Bergmannsheil,
Ruhr-University Bochum, Bochum, Germany

for their respective contributions to the pediatric and surgical ICU chapters of 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 viral diseases and other medical conditions, assessing disease severity and prognosis, and guiding clinical decisions on antibiotic therapy.

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 diagnostic cut-offs according to clinical settings.

CHAPTER 2: The diagnostic and prognostic properties of PCT are discussed with examples from clinical research studies.

CHAPTER 3: The use of PCT for monitoring patients and guiding decisions for both initiation and duration of antibiotic therapy 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 represents a significant healthcare burden, in terms of treatment costs, but also the increased risk of resistant micro-organisms.

Emerging antimicrobial resistance and the serious issue of *Clostridium difficile* infections calls for more effective efforts to r**educe the unnecessary and prolonged use of antibiotics** in self-limiting non-bacterial and resolving bacterial infections.

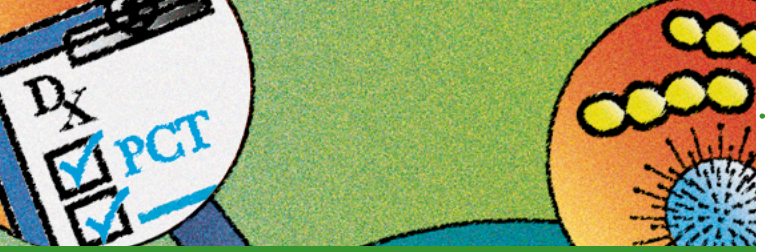
To help achieve this aim, diagnostic tools and biomarkers are urgently needed which allow better assessment of a patient's risk of having an infection, and their response to antibiotic therapy.

One such blood biomarker is procalcitonin (PCT), which is increasingly used in clinical practice for improved patient management. 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 responds adequately to antibiotics [(1)].

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 [(39)]
- 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 [(3)]
- 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 [(3)].

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 protocols, 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 [(4)].



ABOUT PROCALCITONIN

1 What is procalcitonin and where is it produced?

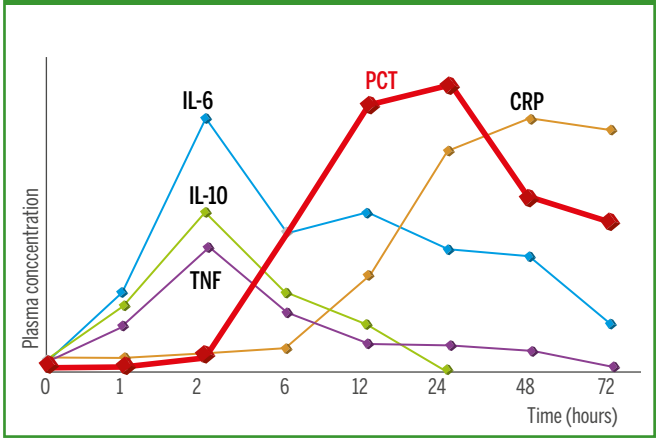
Procalcitonin (PCT) is the precursor peptide – or prohormone – of the mature hormone calcitonin. PCT is released in multiple tissues in response to bacterial infections via a direct stimulation of cytokines [5]. PCT shows an interesting kinetic profile [6].

Cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF) show a fast initial spike upon infection with, however, levels going back 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 its course also has prognostic implications.

Figure 1: Kinetic profiles of different biomarkers of bacterial infection.
Adapted from Meisner M. Procalcitonin: Experience with a new diagnostic tool for bacterial infection and systemic inflammation. J Lab Med 1999;23:263-72 [1].



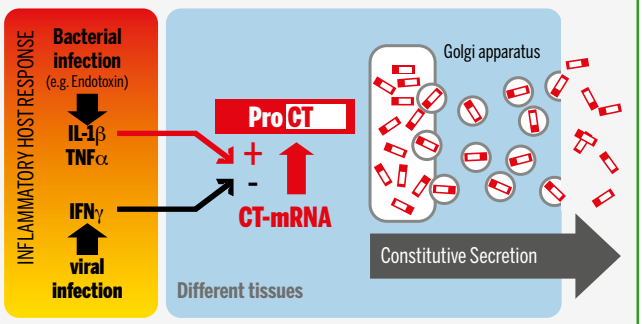
Procalcitonin has an interesting kinetic profile which allows monitoring of the individual patient's response to antimicrobial therapy.

2 How is procalcitonin regulated on a cellular level?

PCT production is induced in response to microbial toxins and to certain bacterial-induced 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**).

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 viral infections**.

Figure 2: Schematic diagram of the regulation of CALC-I gene expression leading to PCT release in cells during septic conditions.
Adapted from Christ-Crain M et al. Swiss Medical Weekly 2005;135(31-32):451-460 [7].
Pro-CT: Prohormone of calcitonin. CT-mRNA: Calcitonin-messenger ribonucleic acid



Procalcitonin is upregulated in response to bacterial but not viral infections, making it a more specific biomarker for bacterial infections. This is helpful for differentiation of viral from 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 rather have mild viral infections.

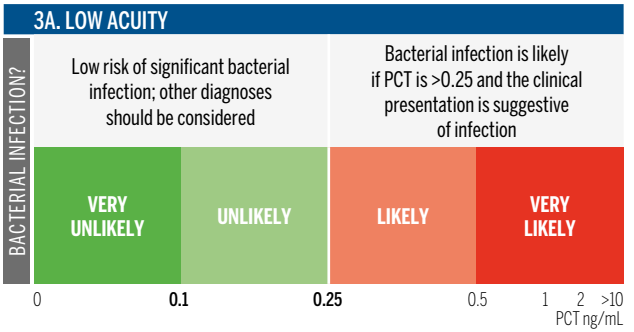
For optimal performance, PCT cut-off values should be adapted to patient acuity (risk level) and clinical setting [8].

IN LOW-ACUITY PATIENTS (Figure 3A), 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.

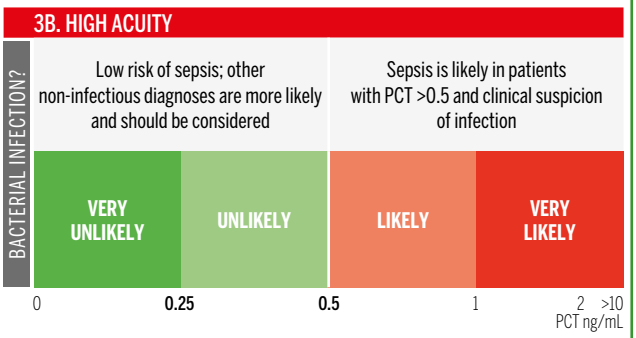
IN HIGH-ACUITY PATIENTS (Figure 3B), typically patients transferred to the **intensive care unit** (ICU), PCT cut-offs of **0.5 ng/mL or 0.25 ng/mL** should be used. PCT levels below these cut-offs make severe bacterial infections and sepsis very unlikely and other diagnoses explaining the patients' 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 [4] and Albrich WC et al. Arch Intern Med. 2012;172(9):715-722 [69]

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.



DIAGNOSTIC AND PROGNOSTIC USE OF PROCALCITONIN

1 Influence of viral and different types of bacterial infections on PCT levels

Since PCT is mainly up-regulated in bacterial infections, it helps to **distinguish viral 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 emergency department patients with clinical signs of a respiratory infection and a low PCT level [10, 11]. This indicates that, in this population, a **low PCT level is helpful to rule out bacterial infections** requiring antibiotic therapy.

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 micro-organism 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 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.

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 viral 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, less than 1% of patients had a positive blood culture when their initial PCT level was <0.25 ng/mL, which increased to >20% in patients with PCT >1.0 ng/mL [13]. However, it seems that 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) [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, as with increasing PCT concentrations, a relevant and serious bacterial infection becomes likely. Conversely, an alternative diagnosis becomes more likely if PCT levels remain low.

2 Diagnostic value of procalcitonin in the early recognition of sepsis

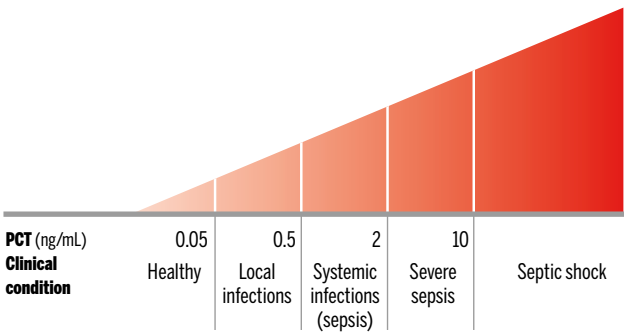
Globally, an estimated 20 - 30 million cases of sepsis occur each year, with over 6 million cases of neonatal and early childhood sepsis, and the rate of sepsis mortality remains unacceptably high (between 30 and 60% of patients with sepsis die) [15]. Furthermore, sepsis has significantly increased by 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, lack of access to vaccines and timely treatments [16].

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, 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 infections, improve 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. Thereby, **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 blood culture proof of bacterial infection and sepsis [4]. Usually, PCT levels are found to be >0.5 ng/mL or higher if patients have bacterial infections leading to sepsis. (**Figure 4**)

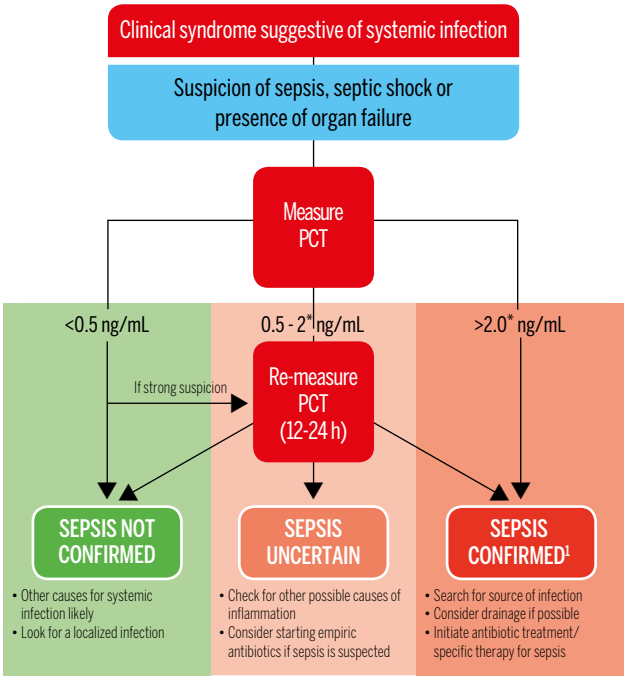
Figure 4: Increasing PCT levels reflect continuous progression from a healthy condition to sepsis and septic shock
Adapted from Meisner M., et al. J Lab Med. 2000;24:076-085 [18].



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 and a PCT level of <0.5 ng/mL 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 page 35 for new definitions of sepsis published in 2016, which abandoned the notion of Systemic Inflammatory Respiratory Syndrome (SIRS), and considered the term severe sepsis to be redundant.

Figure 5: Sepsis diagnosis with PCT in ICU setting
Adapted from Harbarth S, et al. Am J. Resp. Crit. Care Med. 2001;164:396-402 [17]



*The cut-off of 2 ng/mL is given for orientation only. Depending on the patient's background, it may be higher or lower than 2 ng/mL e.g. major surgery (higher) or patient in medical ICU (lower).

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

- **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.**

3 Prognostic value of procalcitonin 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 [19]:

IN LOW-ACUITY PATIENTS WITH RESPIRATORY INFECTIONS:

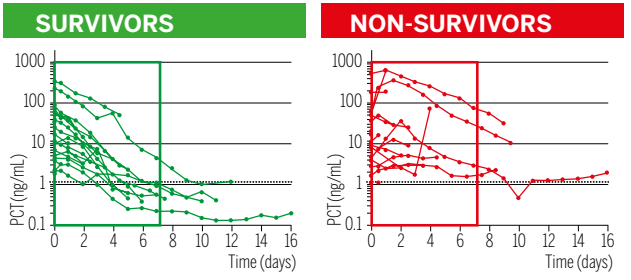
a) a **low PCT level** identifies patients at lower risk for a bacterial etiology and CAP and thus low mortality;

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. 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 [20-23].

Figure 6: Daily variations of PCT levels during ICU hospitalization in patients admitted with sepsis and septic shock that survived or did not survive.
Adapted from Harbarth S., et al. Am J Respir Crit Care Med. 2001;164:396-402 [17].

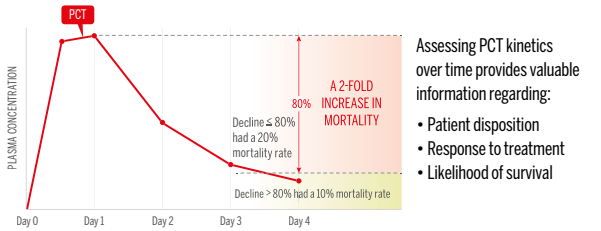


The **Procalcitonin MOnitoring SEpsis Study (MOSES)** has helped expand the clinical utility of PCT. In this study, PCT is used to help assess the response of septic patients to treatment by comparing a baseline PCT measurement with a PCT value taken on day four [24, 25]. **Monitoring the change in PCT 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 7**).

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 7. Using PCT kinetics to assess mortality risk over time.
Adapted from Schuetz P, et al. Crit Care Med. 2017; 45(5):781–789 [25]



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 procalcitonin in neonates and pediatrics

PCT is a very useful biomarker in pediatric populations. The recent **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 LRTI** [26, 71]. In association with clinical signs, PCT measurements can help physicians in the following situations:

■ ANTIBIOTIC GUIDANCE

In a European 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 Lower Respiratory Tract Infections by reducing the duration of antibiotic treatment by almost 2 days (4.5 days in PCT group *vs* 6.3 days in control group) [26]. This effect was most pronounced in pneumonia patients (9.1 days in PCT group *vs* 5.7 days in control patients).

In India, a study in a pediatric ICU has shown that PCT measurements can help rule out sepsis and limit antibiotic use. Antibiotics could be de-escalated in 7.7% of patients and 21% did not require escalation based on a single PCT measurement (with cut-off <2 ng/mL) [27].

In another 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 [28].

■ DIFFERENTIATION OF VIRAL/BACTERIAL 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 bacterial meningitis [29]. This approach/strategy helps avoid unnecessary antibiotic treatments and reduce length of hospital stay in children with viral meningitis.

■ FEBRILE URINARY TRACT INFECTIONS

PCT can help in the diagnosis of acute pyelonephritis and prediction of renal scars, as a PCT level ≥0.5 ng/mL is associated with renal damage and is significantly higher in children with renal scars. A PCT value ≥0.5 ng/mL is associated with high-grade (≥3) vesico-ureteral reflux (VUR) [30].

■ DIAGNOSIS OF SEVERE BACTERIAL INFECTIONS (SBI) IN CHILDREN ≥3 MONTHS WITH FEVER WITHOUT SOURCE (FWS)

A PCT cut-off of 0.5 ng/mL has been suggested to enable early differentiation of SBI and non-severe or viral infections in children with FWS. A risk index score, **the Lab-score**, associating CRP, procalcitonin and urinary dipstick also seems to be a useful tool to predict SBI [31].

■ PREDICTION OF PNEUMOCOCCAL PNEUMONIA

Elevated PCT and CRP in combination with a positive pneumococcal urinary antigen are reliable predictors of pneumococcal pneumonia [32].

DIAGNOSTIC AND PROGNOSTIC USE OF PROCALCITONIN

■ NEONATES

In neonates, PCT levels are physiologically increased and vary depending on hours of age during the first two days of life (**Table 1**) [33].

Table 1: PCT levels in neonates
Adapted from Chiesa et al. Clin Chim Acta 2011;412 (11-12):1053-9 [33].

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

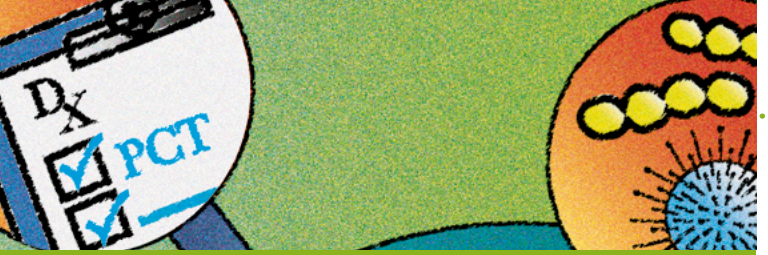
Serum PCT levels at presentation have very good diagnostic accuracy (AUC=0.87) for the diagnosis of neonatal sepsis [34]. In a large prospective study on neonates, **PCT was shown to be the best marker for identifying bacteremia and bacterial meningitis in febrile infants** 7 days to 3 months old [35]

Several randomized intervention studies have shown that the use of a PCT-guided protocol **can shorten antibiotic therapy** in **suspected neonatal early-onset sepsis**. In 2010, a single-center study found that PCT-guided decision-making could result in a shortening of 22.4 h of antibiotic therapy [32]. The recent **multi-center NeoPIns study involving over 1,700 neonates** further demonstrated that PCT-guided decision making can significantly reduce the duration of antibiotic therapy (55 h vs 65 h with standard care) [71].

Elevated umbilical **blood cord PCT concentration** has been described as an independent risk factor of mortality in preterm infants [36]. Lencot *et al.* evaluated the diagnostic value of an umbilical blood cord PCT-based protocol in newborns suspected of Early Onset Neonatal Infections (EONI) [37].

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 should be confirmed by a multicentric validation study.

In the pediatric setting, PCT contributes to early diagnosis, prognosis, therapeutic management and antibiotic guidance.
It can help avoid unnecessary hospitalization and antibiotic exposure in children with viral meningitis or low risk of bacterial infection.



USING PROCALCITONIN 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**[3,8].

1 Use of procalcitonin in Primary Care

Differentiation between viral and bacterial origin of infection in low-acuity patients presenting with symptoms of upper and lower respiratory infections in the primary care setting, remains a difficult task.

A PCT strategy for guiding antibiotic therapy 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).[73] It demonstrated that **PCT-guided treatment significantly improved clinical outcomes in patients with ARIs from different clinical settings** (Figure 8).

- **Mortality at 30 days** was significantly lower in PCT-guided patients than in control patients (8.6% *vs*. 10.0%, 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≤ 0.001) 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≤0.001).

Figure 8: 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[73]

	PCT ng/mL	Control (n = 3372)	PCT ng/mL
30 day mortality	286 (8.6%)	336 (10.0%)	0.037
Total antibiotic exposure, days (*mean*)	5.7	8.1	<.0001
Antibiotic-related side effects	16%	22%	<.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 (Figure 8).

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

Lower respiratory tract infections (LRTI), such as community acquired pneumonia (CAP), bronchitis or exacerbation of chronic obstructive pulmonary disease (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.

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, page 21**).

This concept has been investigated in different trials including more than 1,000 patients with bronchitis and COPD exacerbation [3]. 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

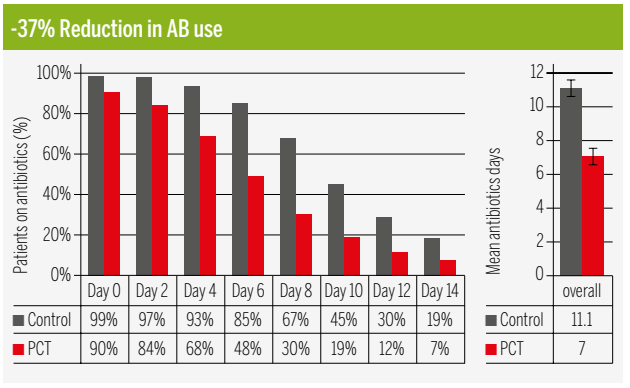
The greatest amount of clinical evidence for using PCT for antibiotic decisions is derived from randomized antibiotic stewardship trials involving over 2,000 patients with community-acquired pneumonia (CAP) [3].

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 **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. 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 nearly 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. Clin Infect Dis 2012 [3].



	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 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 <0.1 ng/mL or even 0.1 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 [8].

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 Lower Respiratory Tract Infections (LRTI) in the Emergency Department and physician offices, of which 1,520 had a final diagnosis of LRTI [69].

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.
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 from Albrich WC, et al. Arch Intern Med. 2012;172(9):715-722 [69].

PCT result (ng/mL)	<0.1	0.1 - 0.25	0.26 - 0.5	>0.5
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 <0.1 ng/L**: CAP PSI V (>130) or CURB-65 >3 points, COPD GOLD IV;
   (b) PCT 0.1-0.25 ng/L: 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, ≥0.5 ng/mL 5 d, ≥1 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

3 Use of procalcitonin in Critical Care

SEPSIS IN THE ICU

The **Stop Antibiotics on Procalcitonin 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.

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 [39].

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 [40].

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**.

The review also supports the use of PCT-based protocols, such as those recommended by Schuetz *et al* [8].

- 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** [40]. 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** is diagnostic of sepsis with a high specificity and high Positive Predictive Value (PPV), and **antibiotic therapy should be started immediately** [40].
  Careful clinical evaluation and periodic monitoring (every 1- 2 days) of PCT levels after antibiotic initiation is an appropriate strategy in these patients [8]. (**Figure 11**).
- **A drop of PCT to <0.5 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 [8, 40].
- **If PCT levels do not decrease by about 50% every 1-2 days, treatment failure should be considered** and patient re-assessment is recommended [8].

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 from Schuetz P et al. Arch Intern Med 2011;171(15):1322-1331 (8).

Evaluation at time of admission

PCT result (ng/mL)	<0.25	0.25 - <0.5	0.5 - <1	≥1
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 day		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 - <0.5 or drop by ≥80%	0.5 and drop by <80%	≥1 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	

The use of PCT to decide when to **stop antibiotics based upon 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** [40].

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].

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 suspected 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).

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%) [41].

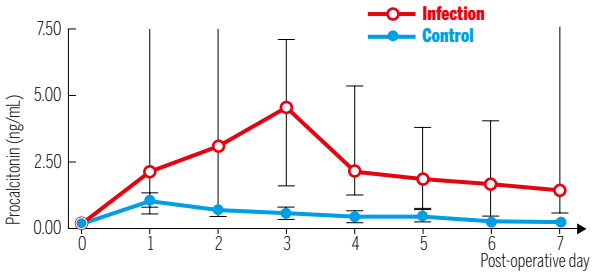
Moreover, in this study, **PCT was found to be more accurate than CRP**, which is still the standard biomarker routinely used in many ICUs.

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. (**Figure 12**) [42].

Figure 12: Comparison of PCT in patients with complicated (infection) and uncomplicated post-operative courses
Adapted from Jebali MA et al. Anesthesiology 2007;107:232-8 [42].



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 [43].

- 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 [44].

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

USING PCT TO GUIDE ANTIBIOTIC THERAPY DECISIONS

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[45].

FREQUENTLY ASKED QUESTIONS

1 Is there an international standard for procalcitonin assays ?

Many procalcitonin (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. 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.

CLINICAL LIMITATIONS OF PCT

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) [46]
- 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 [47]
- invasive fungal infections or acute attacks of *Plasmodium falciparum* [47]
- prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, small cell lung cancer, medullary C-cell carcinoma of the thyroid [47].

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 protocols and used in conjunction with a thorough clinical assessment.

3 What is the value of procalcitonin in immunosuppressed patients ?

Different studies have evaluated the utility of PCT in patients with febrile neutropenia. A systematic review found 30 articles on the topic and concluded that PCT has value as a **diagnostic and prognostic tool in patients with febrile neutropenia**, but that due to differences in patient populations and study qualities, further research is needed [48].

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 including 102 critically ill patients with systemic infections in a medical intensive care unit (ICU) found significantly lower CRP and IL-6 levels, but similar PCT levels, in patients treated with systemic corticosteroids (20 to 1500 mg/day of prednisone parenterally) compared to untreated patients [49].

These observations were confirmed in healthy male volunteers who received different doses of prednisolone up to 30 mg/day before a sepsis-like syndrome was induced with *Escherichia coli* lipopolysaccharide (LPS) injections [50]. While other biomarkers were significantly inhibited in a dose-dependent way, levels of PCT showed no inhibition within the study period.

Observational studies suggest PCT may improve diagnosis in immunosuppressed patients and 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 decision**s due to the high antibiotic costs associated with critically ill patients [51, 52, 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 [70].

Likewise, 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 [53]. 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 [54]. 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 Other applications

PCT AND FUNGAL INFECTIONS

Several studies have demonstrated the potential clinical utility of PCT in predicting invasive fungal infections [55, 56]. 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 [57]. 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 [58]. 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.

GUIDELINES AND RECOMMENDATIONS

Based on the body of literature, national and international guidelines have included the concept of using PCT to confirm or rule out severe bacterial infections, monitor patients and guide antibiotic therapy decisions.

- **The Surviving Sepsis Campaign (SSC) Guidelines** published in 2012 and updated in 2016 advocate that a low PCT level helps to rule out an infection in patients with a systemic inflammatory response syndrome (SIRS). The 2012 SSC Guidelines suggested "the use of low procalcitonin to assist the clinician in the discontinuation of empiric antibiotics when no evidence of infection is found (grade 2C)...". [59] The updated 2016 guidelines now suggest that "measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients". [72]

  In addition, the associated SSC Care Bundles were revised in 2015 in response to new evidence regarding use of central line catheters in the 6-hour bundle [60].

- The **2012 European respiratory guidelines** emphasize that PCT should be used to monitor antibiotic treatment of patients. Specifically, it is stated that
  "...biomarkers can guide treatment duration by the application of predefined stopping rules for antibiotics. It has been shown that such rules work even in most severe cases, including pneumonia with septic shock, and even if clinicians are allowed to overrule the predefined stopping rules" [61].

- The **2011 German sepsis society guidelines recommend using PCT to confirm or rule out a systemic infection** in patients presenting with a clinical suspicion because studies have repeatedly demonstrated that low PCT levels reliably rule out sepsis with a high negative predictive value, while a high PCT levels argues for the presence of infection/ sepsis [62].

- In 2008, the **American College of Critical Care Medicine and the Infectious Diseases Society of America** updated their guidelines for evaluation of new fever in critically ill adult patients and included PCT as a more sensitive test for the early detection of bacterial infections and sepsis in patients during the first day of ICU [64].

- Similarly, **sepsis and emergency department guidelines in Sweden, the US, China, Spain, Brazil and Ireland** have also included PCT [63-67].

NEW DEFINITIONS FOR SEPSIS AND SEPTIC SHOCK

Based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) Singer et al. JAMA. 2016;315(8): 801-810 [68].

- 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 greater than 10% **(Table 2)**.

- **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 or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 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 13)**.

  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

Table 2: The SOFA SCORE Sequential (Sepsis-Related) Organ Failure Assessment Score

Adapted from Singer M. *et al.* JAMA. 2016;315(8):801-810 [68].

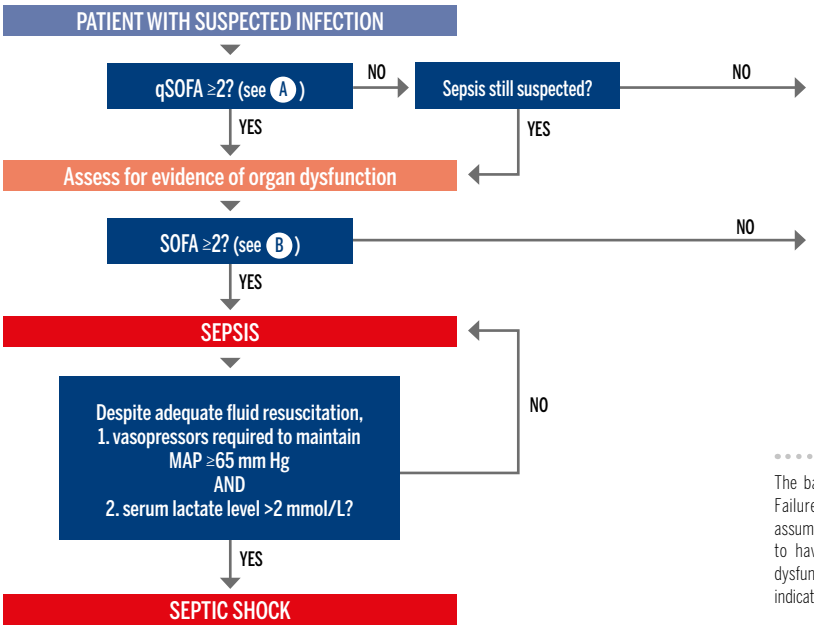
	SCORE				
SYSTEM	0	1	2	3	4
RESPIRATION					
PaO_2/FIO_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
COAGULATION					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
LIVER					
Bilirubin, mg/dL (µmol/L)L	<1.2 (20)	1.2-1.9 (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, mg/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 13: Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock

Adapted from Singer M. et al. JAMA. 2016;315(8):801-810 [68].



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 preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

PCT-BASED PROTOCOLS FOR GUIDANCE OF ANTIBIOTIC THERAPY

The following pages provide guidance for **INITIATING**, **CONTINUING** or **STOPPING** antibiotic therapy in LRTI or septic patients.

The protocols can be extracted from the booklet and kept as a useful reference tool (cut along the dotted line).

Alternatively, use the dedicated slide ruler available on request from bioMérieux.

IMPORTANT: PCT results do not replace clinical assessment and judgment. For clinical limitations of PCT, see page 29.

Procalcitonin-based protocol for decision to **START ANTIBIOTICS** for patients presenting with suspected or confirmed LRTI*

Adapted from Albrich WC, et al. Effectiveness and Safety of Procalcitonin-Guided Antibiotic Therapy in Lower Respiratory Tract Infections in "Real Life": An International, Multicenter Post-study Survey (ProREAL). Arch Intern Med. 2012;172(9):715-722

BIOMÉRIEUX

PCT results do not replace clinical assessment and judgment.

* LRTI: Lower Respiratory Tract Infection

** **HIGH-RISK LRTI**:** Intensive Care Units. Severe pneumonic infections (high mortality risk).

PATIENT PRESENTING WITH CLINICAL SYMPTOMS OF LRTI

↓

PERFORM CLINICAL ASSESSMENT

↓

Perform PCT test

PCT test result on presentation (ng/mL)	<0.1	0.1 - 0.25	0.26 - 0.5	>0.5
Decision to START ANTIBIOTIC THERAPY	ANTIBIOTIC THERAPY STRONGLY DISCOURAGED	ANTIBIOTIC THERAPY DISCOURAGED	ANTIBIOTIC THERAPY RECOMMENDED	ANTIBIOTIC THERAPY STRONGLY RECOMMENDED
Over-riding rules	CONSIDER ABX IF PATIENT IS CLINICALLY UNSTABLE, STRONG SUSPICION OF PNEUMONIA OR HIGH-RISK**			
Follow-up comments	IF NO CLINICAL IMPROVEMENT, CLINICAL RE-EVALUATION ADVISED		CLINICAL RE-EVALUATION ADVISED	
Repeat PCT test	REPEAT PCT WITHIN 6 - 24 HOURS		REPEAT PCT EVERY 2 - 3 DAYS CONSIDER STOPPING ANTIBIOTICS EARLIER	

SEE OVERLEAF FOR GUIDANCE ON CONTINUING OR STOPPING ANTIBIOTIC THERAPY

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 <0.1 ng/L**: CAP PSI V (>130) or CURB-65 >3 points, COPD GOLD IV;
   (b) PCT 0.1-0.25 ng/L: 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

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; PSI, Pneumonia Severity Index; SCLC, TB, tuberculosis

Procalcitonin-based protocol for decision to **CONTINUE** or **STOP ANTIBIOTICS** for patients with confirmed LRTI*

Adapted from Albrich WC, et al. Effectiveness and Safety of Procalcitonin-Guided Antibiotic Therapy in Lower Respiratory Tract Infections in "Real Life": An International, Multicenter Post-study Survey (ProREAL). Arch Intern Med. 2012;172(9):715-722

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PCT results do not replace clinical assessment and judgment.

* LRTI: Lower Respiratory Tract Infection

** **HIGH-RISK LRTI***: Intensive Care Units. Severe pneumonic infections (high mortality risk).

LRTI PATIENT ON ANTIBIOTIC THERAPY

Repeat PCT test every 2 - 3 days

PCT test result on follow-up (ng/mL)	<0.1	0.1 - 0.25	0.26 - 0.5	>0.5
Decision to CONTINUE or STOP ANTIBIOTIC THERAPY	STOPPING ANTIBIOTIC THERAPY STRONGLY ENCOURAGED if clinical improvement	STOPPING ANTIBIOTIC THERAPY ENCOURAGED if clinical improvement	CONTINUING ANTIBIOTIC THERAPY RECOMMENDED	CONTINUING ANTIBIOTIC THERAPY STRONGLY RECOMMENDED
Over-riding rules	CONTINUE ABX IF PATIENT IS CLINICALLY UNSTABLE, STRONG SUSPICION OF PNEUMONIA OR HIGH-RISK**			
Follow-up comments	IF NO CLINICAL IMPROVEMENT, CLINICAL RE-EVALUATION ADVISED		CLINICAL RE-EVALUATION ADVISED	
Repeat PCT test	REPEAT PCT AFTER 1 - 2 DAYS		REPEAT PCT EVERY 2 - 3 DAYS	
			IF PCT REMAINS HIGH, TREATMENT FAILURE LIKELY	

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, ≥0.5 ng/mL 5 d, ≥1 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; MOF, multiple organ failure; SCLC, small-cell lung cancer; SIRS, sepsis inflammatory response syndrome

Procalcitonin-based protocol for decision to **START ANTIBIOTICS** for patients with suspected **SEPSIS** in **INTENSIVE CARE UNITS**[1,2,3]

Adapted from Bouadma L, *et al*. Lancet 2010[1] and Schuetz P, *et al*. Arch Intern Med. 2011[2] with recommendations to consider antibiotic treatment to maximize patient safety.[2,3]

References: 1. Bouadma L, *et al*. Lancet 2010;375:463-74. ■ 2. Schuetz P, et al. Arch Intern Med. 2011;171:1322-1331. ■ 3. Rhodes A, *et al*. Critical Care Medicine 2017; 45(3):486–552

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PATIENT PRESENTING WITH CLINICAL SIGNS OF SEPSIS

PERFORM CLINICAL ASSESSMENT

⚠ START EMPIRIC ANTIBIOTIC THERAPY IMMEDIATELY, IF SEPSIS IS STRONGLY SUSPECTED

Perform PCT test

PCT test result at time of admission (ng/mL)	<0.25	0.25 - <0.5	0.5 - <1.0	≥1.0
Decision to START ANTIBIOTIC THERAPY	ANTIBIOTIC THERAPY STRONGLY DISCOURAGED	ANTIBIOTIC THERAPY DISCOURAGED	ANTIBIOTIC THERAPY ENCOURAGED	ANTIBIOTIC THERAPY STRONGLY ENCOURAGED
Follow-up comments	CLINICAL RE-EVALUATION ADVISED. CONSIDER ALTERNATIVE DIAGNOSIS		CLINICAL RE-EVALUATION ADVISED	
Repeat PCT test	REPEAT PCT AFTER 6 - 24 HOURS		REPEAT PCT EVERY 1 - 2 DAYS	
	SEE OVERLEAF FOR GUIDANCE ON CONTINUING OR STOPPING ANTIBIOTIC THERAPY			

Procalcitonin-based protocol for decision to CONTINUE or STOP ANTIBIOTICS for patients with SEPSIS in INTENSIVE CARE UNITS [1,2,3]

Adapted from Bouadma L, *et al*. Lancet 2010[1] and Schuetz P, *et al*. Arch Intern Med. 2011[2] with recommendations to consider antibiotic treatment to maximize patient safety.[2,3]
References: 1. Bouadma L, *et al*. Lancet 2010;375:463-74. ■ 2. Schuetz P, *et al*. Arch Intern Med. 2011;171:1322-1331. ■ 3. Rhodes A, *et al*. Critical Care Medicine 2017; 45(3):486–552

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PCT results do not replace clinical assessment and judgment.

SEPTIC PATIENT ON ANTIBIOTIC THERAPY

Repeat PCT test

PCT test result on follow-up (ng/mL)	<0.25 or PCT level ↘ by > 90%*	0.25 - <0.5 or PCT level ↘ by ≥80%*	≥0.5 and PCT level ↘ by < 80%	≥1.0 and PCT level ↗
Decision to CONTINUE or STOP ANTIBIOTIC THERAPY	STOPPING ANTIBIOTIC THERAPY STRONGLY ENCOURAGED if clinical improvement	STOPPING ANTIBIOTIC THERAPY ENCOURAGED if clinical improvement	CONTINUING ANTIBIOTIC THERAPY ENCOURAGED	CONTINUING ANTIBIOTIC THERAPY STRONGLY ENCOURAGED
Over-riding rules	⚠ CONTINUE ANTIBIOTIC THERAPY IF PATIENT IS CLINICALLY UNSTABLE			
Follow-up comments	IF NO CLINICAL IMPROVEMENT, CLINICAL RE-EVALUATION ADVISED		CLINICAL RE-EVALUATION ADVISED	
Repeat PCT test	REPEAT PCT EVERY 1 - 2 DAYS		REPEAT PCT EVERY 1 - 2 DAYS CONSIDER STOPPING ANTIBIOTICS EARLIER	
			IF PCT REMAINS HIGH, TREATMENT FAILURE LIKELY	

* Drop by at least 80% from baseline in patients showing clinical improvement after therapy

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
LRTI	Lower respiratory tract infection
IL	Interleukin
LPS	Lipopolysaccharide
MRSA	Methicillin-Resistant *Staphylococcus 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 S.A. • 69280 Marcy l'Étoile • France
Tel.: + 33 (0)4 78 87 20 00 • Fax: +33 (0)4 78 87 20 90
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