ALSO AVAILABLE:

→ PCT booklets (testimonials and case studies in adult population and pediatric setting)

→ PCT-based algorithm for antibiotic therapy guidance in LRTI/Sepsis

The information in this booklet is given as a guideline only and is not intended to be exhaustive.
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Clinical Guide to Use of
PROCALCITONIN
for Diagnosis and Guidance of Antibiotic Therapy

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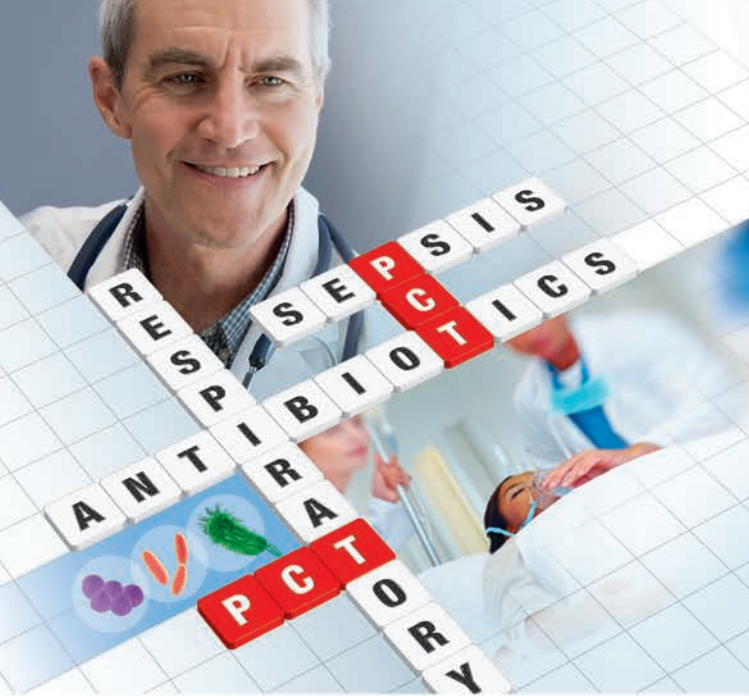
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Preface

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

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 continuous rise in *Clostridium difficile* infections calls for more effective efforts to **reduce the unnecessary and prolonged use of antibiotics** in self-limiting non-bacterial and resolving bacterial infections.

To help achieve this aim, diagnostic tools and biomarkers are urgently needed 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. It has been demonstrated that **PCT improves early detection of sepsis and risk stratification** [2]. Studies on respiratory infections have shown that using PCT to monitor therapy has led to **a more tailored use of antibiotics** with a reduction in antibiotic exposure of 30-70% depending on the clinical setting, and 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 algorithms, PCT provides **additional useful information** and **aids physicians in making rational clinical decisions** in individual patient cases. As with any diagnostic test, knowledge of the strengths and limitations of PCT is a prerequisite for its safe and efficient use in clinical practice [4].

I

BACKGROUND INFORMATION

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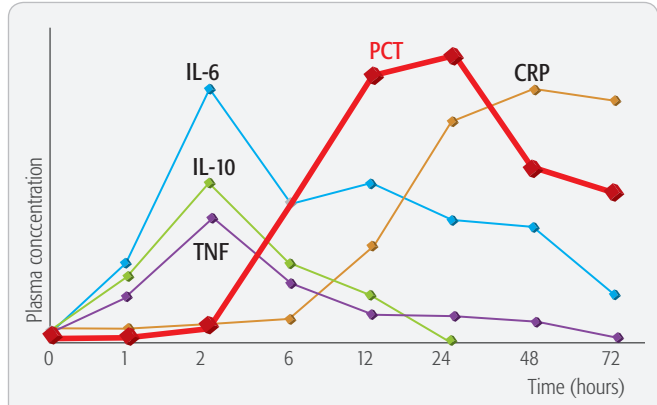
Figure 1: Kinetic profiles of different biomarkers of bacterial infection.
Adapted from Meisner M. Procalcitonin: Experience with a new diagnostic tool for bacterial infection and systemic inflammation. J Lab Med 1999;23:263-72. [1]

> 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.
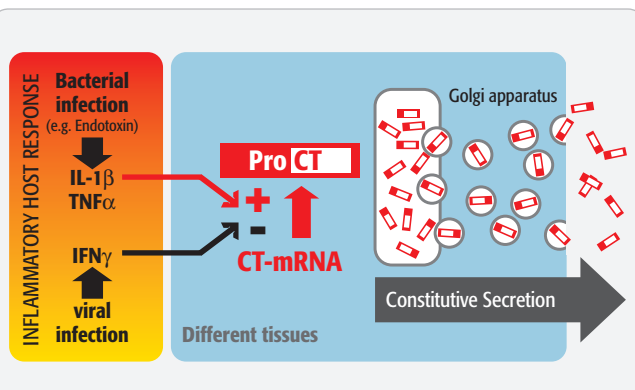
Figure 2: Schematic diagram of the regulation of CALC-I gene expression leading to PCT release in cells during septic conditions.

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.**

Figure 3: PCT cut-off levels adapted to acuity.
Adapted from Schuetz P *et al.* BMC Medicine 2011;9:107. [4]

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

| 3A. LOW ACUITY			
Low risk of significant bacterial infection; other diagnoses should be considered		**Bacterial infection is likely if PCT is >0.25 and the clinical presentation is suggestive of infection**	
VERY UNLIKELY	**UNLIKELY**	**LIKELY**	**VERY LIKELY**

BACTERIAL INFECTION?

0   0.1   0.25   0.5   1   2   >10
PCT ng/mL

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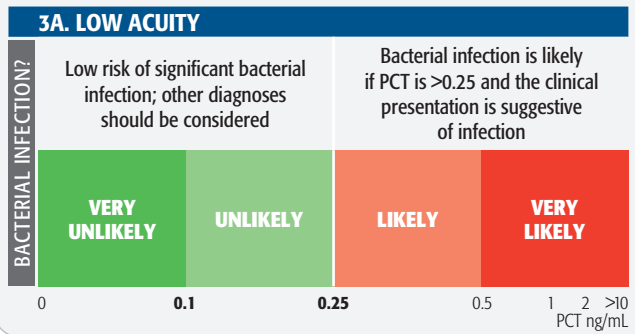
HIGH ACUITY refers to patients transferred to the intensive care unit because of severe disease.

3B. HIGH ACUITY			
Low risk of sepsis; other non-infectious diagnoses are more likely and should be considered		**Sepsis is likely in patients with PCT >0.5 and clinical suspicion of sepsis**	
VERY UNLIKELY	**UNLIKELY**	**LIKELY**	**VERY LIKELY**

BACTERIAL INFECTION?

0   0.25   0.5   1   2   >10
PCT ng/mL
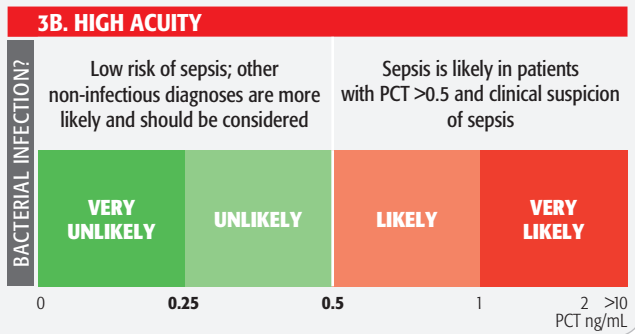
DIAGNOSTIC AND PROGNOSTIC USE OF PROCALCITONIN

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 in most cases a viral infection. Yet, it significantly increases in patients with bacterial pneumonia [9].

In line with this, 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 a **low PCT level is helpful to rule out bacterial infections** which warrant antibiotic therapy in this population.

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 positive blood culture when their initial PCT level was <0.25 ng/mL, which increased to >20% in patients with PCT >2.5 ng/mL [13]. However, it seems that PCT may not help to reliably predict the type of bacterial 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 occurs 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].
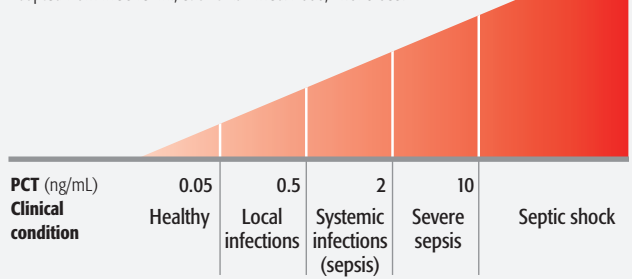
The cornerstone of today's sepsis treatment is **early recognition of the condition** and **early initiation of appropriate antibiotic therapy**, as well as **fluid resuscitation**. Clinical signs, such as the systemic inflammatory response syndrome (SIRS) criteria, lack both sensitivity and specificity. 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 severe sepsis and septic shock
Adapted from Meisner M., *et al.* J Lab Med. 2000;24:076-085. [18]

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

IN THE ICU SETTING and in **patients with suspicion of severe 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 enables the **diagnostic differentiation between various clinical conditions mimicking severe systemic bacterial infections and sepsis**.

> **Procalcitonin is most promising for early detection of patients at risk for sepsis and bacteremia:**
> ■ **Low procalcitonin** levels may help to rule out sepsis and help physicians focus on other medical conditions.
> ■ **High levels** confirm that sepsis is very likely.

Fever, leukocytosis, hypotension, etc.

Suspicion of sepsis, severe sepsis or septic shock [1]

1) In the absence of non-infectious causes for induction of PCT

Measure PCT

<0.5 ng/mL   ≥0.5 - <2* ng/mL   ≥2* ng/mL

If strong suspicion

Re-measure PCT (12-24 h)

SEPSIS NOT CONFIRMED
• Other causes for systemic infection likely
• Look for a localized infection

SEPSIS UNCERTAIN
• Check for other possible causes of inflammation

SEPSIS CONFIRMED [1]
• Search for source of infection
• Consider drainage if possible
• Initiate antibiotic treatment/specific therapy for sepsis

* 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).

Figure 5: Sepsis diagnosis with PCT in ICU setting
Source : Thermo Fisher Scientific communication "Guide for the Clinical Use of Procalcitonin (PCT).

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 ethology 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 ethology 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].

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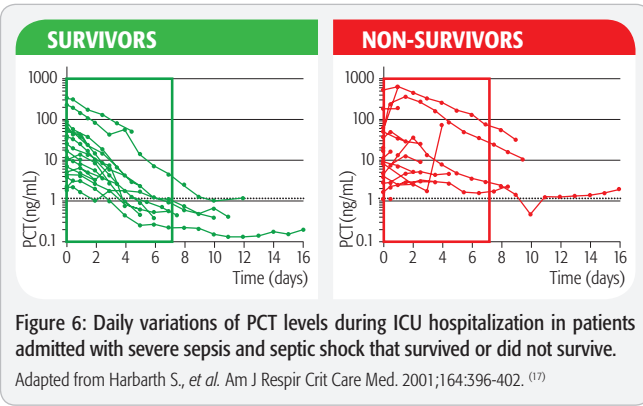
Figure 6: Daily variations of PCT levels during ICU hospitalization in patients admitted with severe sepsis and septic shock that survived or did not survive.
Adapted from Harbarth S., *et al.* Am J Respir Crit Care Med. 2001;164:396-402. [17]

4 | Differentiation of heart failure and lung infection

The diagnosis of pneumonia may be difficult in patients with pre-existing parenchymal lung disease because of baseline abnormal chest imaging. Detecting superimposed pneumonia in patients presenting with acute heart failure is additionally difficult because of the non-specific nature of chest X-ray abnormalities in the setting of cardiogenic pulmonary edema.

A recent trial (BACH) including 1,641 patients presenting to the ED with dyspnea found PCT helpful in such cases of high diagnostic uncertainty [24], which constituted 30% of the patient population. In fact, **combining physician estimates of the probability of pneumonia with PCT values significantly increased the accuracy for the diagnosis of pneumonia in all patients presenting with dyspnea**. In addition, patients with a diagnosis of acute heart failure (AHF) and an elevated PCT concentration had a worse outcome if not treated with antibiotics, while patients with low PCT values had a better outcome if they did not receive antibiotic therapy (**Figure 7**).

> ▶ In patients with acute dyspnea, PCT significantly increases the accuracy of diagnosis of pneumonia, thereby helping to differentiate acute heart failure from respiratory infection in cases of high diagnostic uncertainty.
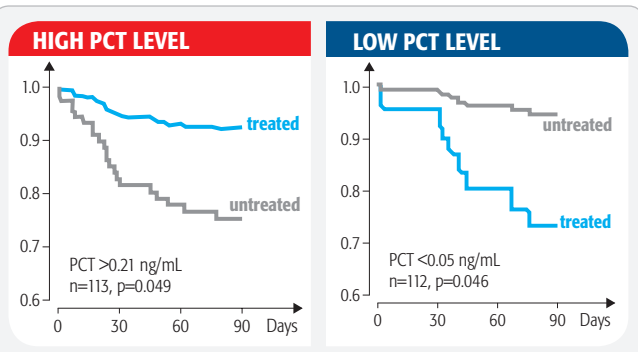
Figure 7: Kaplan–Meier plot for antibiotic treatment and all-cause mortality within 90 days for patients with acute heart failure and subgrouped by procalcitonin (PCT) quintiles: PCT . 0.21 ng/mL (highest quintile, P = 0.049) and,0.05 ng/mL (lowest quintile, P = 0.046)

Adapted from Maisel A. *et al.*, Eur J Heart Fail. 2012;14(3):278-86. [24]

5 Use of procalcitonin in neonates and pediatrics

In the pediatric population, PCT is a very useful biomarker, which can **help physicians** in association with clinical signs in the following situations:

■ DIFFERENTIATION OF VIRAL/BACTERIAL MENINGITIS

A PCT level ≥ 0.5 ng/mL associated with a CSF protein level ≥ 0.5 ng/mL and interpreted with clinical rules is a sensitive and specific marker to identify bacterial meningitis [25]. 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) [26].

■ 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 [27].

■ PREDICTION OF PNEUMOCOCCAL PNEUMONIA

Elevated PCT and CRP in combination with a positive pneumococcal urinary antigen are reliable predictors of pneumococcal pneumonia [28].

■ ANTIBIOTIC GUIDANCE

In the largest randomized trial on antibiotic use in children, the use of a PCT cut-off of 0.25 µg/L 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].

■ NEONATES

Normal PCT values in infants are <0.05 ng/mL.

In neonates, PCT levels are physiologically increased and vary depending on hours of age during the first two days of life (**Table 1**) [30].

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

Table 1: PCT levels in neonates

Adapted from Chiesa *et al.* Clin Chim Acta 2011;412 (11-12):1053-9. [30]

Serum PCT levels at presentation have very good diagnostic accuracy (AUC=0.87) for the diagnosis of neonatal sepsis [31]. The use of a PCT-guided algorithm can shorten antibiotic therapy in suspected neonatal early-onset sepsis [29]. However, these findings need to be confirmed in a larger cohort of neonates.

Finally, elevated umbilical blood cord procalcitonin concentration has been described as an independent risk factor of mortality in preterm infants [32].

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

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** [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, and
- **reassuring patients** that antibiotics are not necessary.

Randomised trials including more than 1,000 patients have shown a reduction of antibiotic exposure by more than 60% when PCT was used to guide antibiotic initiation in the primary care setting (**Figure 8**) [3].

Importantly, there was no increase in the risk of mortality, relapse or treatment failure in patients, and time to recovery was similar in both groups.

Based on this evidence:

- **in patients with a low pre-test probability** for a bacterial infection, a single PCT measurement and a value below the cut-off of **<0.25 ng/mL or certainly <0.1 ng/mL** appears to be **safe to exclude a relevant bacterial infection** and to therefore decide not to initiate antibiotic therapy (**Figure 9**) [8].
- **clinical follow up** with re-measurement of PCT within 6-24 hours should be considered in all patients who show clinical deterioration.
- **if PCT is >0.25 ng/mL, and particularly >0.5 ng/mL**, a bacterial infection becomes likely and clinicians should consider expanding their diagnostic assessment, **offering antibiotic therapy**, and more closely monitoring the patient.

-65% Reduction in AB use

	Day 0	Day 2	Day 4	Day 6	Day 8	Day 10	Day 12	Day 14		overall
Control	63%	63%	59%	43%	14%	4%	3%	1%	Control	4.6
PCT	23%	21%	19%	13%	6%	2%	1%	0%	PCT	1.6

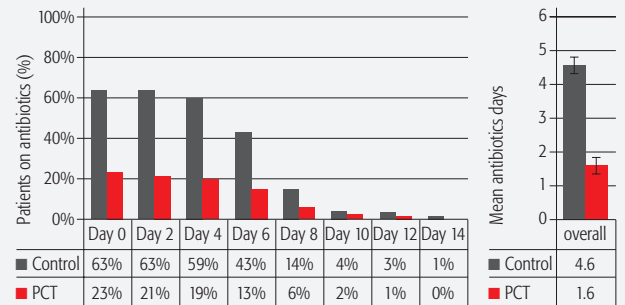Figure 8: Antibiotic use in primary care with (red) and without (grey) PCT guidance. Adapted from Schuetz P *et al*. Clin Infect Dis. 2012;55:651-62. [3]

> With PCT guidance, only **23% of patients** were given antibiotics *vs* 63% in the control group. The mean duration of treatment was **1.6 days** in the PCT group *vs* 4.6 days in the control group, indicating a reduction in antibiotic exposure of over 60% (**Figure 8**).

Figure 9: Proposed algorithm for use of PCT values to determine antibiotic treatment in **LOW-ACUITY NON-PNEUMONIC INFECTIONS** (ie, low risk) in primary care and emergency department settings.
Adapted from Schuetz P et al: Arch Intern Med 2011;171:1322-31. [8]

Evaluation at time of admission				
PCT result (ng/mL)	< 0.1	0.1 - < 0.25	0.25 - < 0.5	≥ 0.5
Recommendation regarding use of Abx	STRONGLY DISCOURAGED	DISCOURAGED	ENCOURAGED	STRONGLY ENCOURAGED
Overruling the algorithm	Consider use of antibiotics if patients are clinically unstable, have strong evidence of pneumonia, are at high risk (i.e., COPD GOLD III-IV), or need hospitalization			
Follow-up/ other comments	Follow-up only needed if no symptom resolution after 1 to 2 days ; if clinical situation is not improving; consider Abx if PCT level increases to ≥0.25 µg/L		Clinical reevaluation as appropriate	

▶ In low-acuity patients with upper and lower respiratory infections in primary care, an initial PCT level measurement helps rule out bacterial infection and therefore exclude the need for empiric antibiotic therapy.

2   Use of Procalcitonin in ED and in-patients

■ BRONCHITIS, COPD EXACERBATION IN THE ED

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

Studies have evaluated PCT protocols in these patients and found that for patients who are clinically stable and are treated at the ED or are hospitalized, the **initiation of antibiotic therapy** should be based on **clinical grounds** and a **PCT value of ≥0.25 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 11, 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 overruling condition is present.

In severe COPD, empiric therapy may still be considered initially in high-acuity patients.

■ COMMUNITY ACQUIRED PNEUMONIA IN THE ED

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 a**ntibiotic 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 10**).

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.

-37% Reduction in AB use

	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
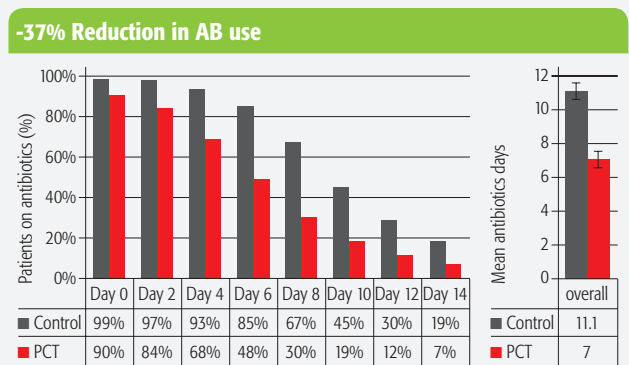
Figure 10: Antibiotic use in CAP patients with (red) and without (grey) PCT guidance.
Adapted from Schuetz P, *et al.* Clin Infect Dis 2012;55:651-62. [3]

> 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 10**).

In patients suspected of having a pneumonia based on the presence of infiltrates, a **persistent (over 24-48 hrs.) PCT level of <0.1 ng/mL** or even 0.1 ng/mL to < 0.25 ng/mL **argues against a typical bacterial infection**. Physicians should then consider 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.

If antibiotics are withheld initially, PCT should be rechecked after 6-24 hours. If PCT levels are <0.25 ng/mL, but bacterial infection is still highly suspected based on the clinical presentation or microbiological results, antibiotic therapy may still be considered, particularly in patients at higher risk for adverse outcome. **If PCT remains low during follow-up, early discontinuation of antibiotics should be considered as well as an aggressive diagnostic workup for other etiologies. (Figure 11)** [8].

Figure 11: Proposed algorithm for use of PCT values to determine antibiotic treatment in **MODERATE-ACUITY PNEUMONIC INFECTIONS** (ie, moderate risk) in hospital and ED settings.
Adapted from Schuetz P et al. Arch Intern Med 2011;171(15):1322-31. [8]

Evaluation at time of admission				
PCT result (ng/mL)	**< 0.1**	**0.1 - < 0.25**	**0.25 - < 0.5**	**≥ 0.5**
Recommendation regarding use of Abx	**STRONGLY DISCOURAGED**	**DISCOURAGED**	**ENCOURAGED**	**STRONGLY ENCOURAGED**
Overruling the algorithm	Consider alternative diagnosis, or Abx if patients are clinically unstable, are at high risk for adverse outcome (eg, PSI classes IV-V, immunosuppression), or have strong evidence of a bacterial pathogen			
Follow-up/ other comments	Reassess patients' condition and recheck PCT level after 6 to 12 hours if no clinical improvement is observed		Recheck PCT level every 2 to 3 days to consider stopping Abx	

Follow-up evaluation every 2 to 3 days				
PCT result (ng/mL)	**< 0.1**	**0.1 - < 0.25**	**0.25 - < 0.5**	**≥ 0.5**
Recommendation regarding use of Abx	**STOPPING ABx STRONGLY ENCOURAGED**	**STOPPING ABx ENCOURAGED**	**CONTINING ABx ENCOURAGED**	**CONTINING 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	

> In community-acquired pneumonia (CAP), monitoring the course of PCT helps shorten the duration of treatment.

3 Use of Procalcitonin in Critical Care

■ SEPSIS IN MEDICAL ICU

For highest acuity patients with a strong suspicion of severe bacterial infection, **empiric antibiotic therapy should not be delayed**. Nevertheless, an initial PCT level of <0.5 ng/mL argues strongly against a bacterial infectiotn and other diagnoses should be considered, including viral etiologies.

A careful clinical evaluation and periodic monitoring (every 1-2 days) of PCT levels after antibiotic initiation appears to be an appropriate strategy in these patients (**Figure 12**).

- **A drop of PCT to <0.5 ng/mL or by at least 80-90%** from peak values are reasonably conservative thresholds for **stopping antibiotic therapy** in this fragile population, assuming patients also show a favorable clinical response [8].

- **If PCT levels do not decrease by about 50% every 1-2 days, treatment failure should be considered** and re-assessment of patients is recommended.

In clinical studies including more than 500 patients from the medical and surgical ICU, such ICU 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 sepsis.

Figure 12: Proposed algorithm 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 - < 1.0	≥ 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 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%	≥ 1.0 and PCT rise
Recommendation regarding use of Abx	STOPPING ABx STRONGLY ENCOURAGED	STOPPING ABx ENCOURAGED	CONTINING ABx DISCOURAGED	CONTINING ABx STRONGLY DISCOURAGED
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 falled if PCT level does not decrease adequately	

■ 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 13**) [33].

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 [34].

- ■ 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 [35].
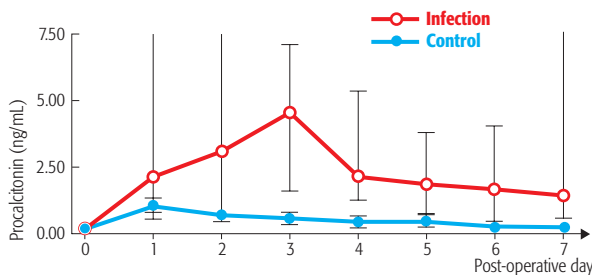
Figure 13: Comparison of PCT in patients with complicated (infection) and uncomplicated post-operative courses
Adapted from Jebali MA *et al.* Anesthesiology 2007;107:232-8. [33]

→ 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 PCT ratio of <1.03 between post-operative days 1 and 2 has been suggested to be highly indicative of unsuccessful elimination of the septic focus. [36]

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

IV

FREQUENTLY ASKED QUESTIONS

1 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.

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

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) [37]
■ 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 [38]
■ invasive fungal infections or acute attacks of *Plasmodium falciparum* [38]
■ prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, small cell lung cancer, medullary C-cell carcinoma of the thyroid. [38]

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.

---

2 What is the value of procalcitonin in immunosuppressed patients ?

Different studies have evaluated the utility of PCT in patients with febrile neutropenia. A recent 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 [39].

Importantly in this regard, **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 [40].

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 [41]. While other biomarkers are 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.

3 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 a cost-saving.

A recent meta-analysis concluded 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 [42, 43].

Furthermore, studies in the ICU setting have shown a reduction in the length of stay of about 1.5 days, which was significant in some but not all studies [43]. In general medical ward patients, length of stay is reduced by about 0.5 days [3].

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, shorter length of stay, reduced risk for side-effects and reduced emergence of multi-resistant bacteria.

GUIDELINES

▶ CURRENT GUIDELINE RECOMMENDATIONS

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

■ The recent **2012 update in the Surviving Sepsis Campaign** now advocates that a low PCT level helps to rule out an infection in patients with a systemic inflammatory response syndrome (SIRS). The Guidelines *"suggest the use of low procalcitonin to assist the clinician in the discontinuation of empiric antibiotics when no evidence of infection is found (grade 2C)…"*. [44]

■ Moreover, the most recent **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*". [45]

■ 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 [46].

■ Similarly, **sepsis and emergency department guidelines in Sweden, the US, China and Spain** have also included PCT [47 - 49]. 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 [47]. The 2007 Spanish guidelines have emphasized the importance of the use of biomarkers for early diagnosis of sepsis and added high plasma levels of PCT to the list of signs and symptoms of sepsis diagnosis [48].

PCT-BASED ALGORITHMS FOR GUIDANCE OF ANTIBIOTIC THERAPY

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

The algorithms 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.
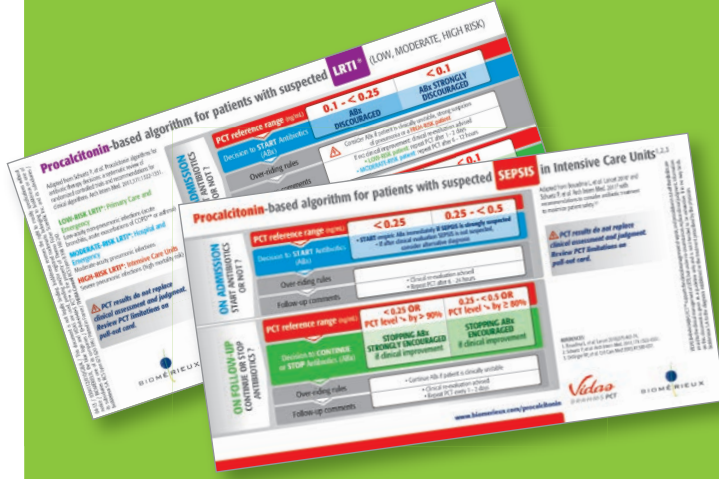
IMPORTANT: PCT results do not replace clinical assessment and judgment. For clinical limitations of PCT, see page 27.

30

Procalcitonin-based algorithm for decision to START ANTIBIOTICS for patients presenting with suspected LOW or MODERATE RISK LRTI*

Source: Schuetz P, et al. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med. 2011;171:1322-31.

⚠ **PCT results do not replace clinical assessment and judgment.**

LOW-RISK LRTI: Primary Care / Emergency
Low-acuity non-pneumonic infections (acute bronchitis, acute exacerbations of Chronic Obstructive Pulmonary Disease (COPD) or asthma)

MODERATE-RISK LRTI: Hospital / Emergency
Moderate-acuity pneumonic infections

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 at time of admission (ng/mL)	<0.1	0.1 - <0.25	0.25 - <0.5	≥0.5
Decision to START ANTIBIOTIC THERAPY	ANTIBIOTIC THERAPY STRONGLY DISCOURAGED	ANTIBIOTIC THERAPY DISCOURAGED	ANTIBIOTIC THERAPY ENCOURAGED	ANTIBIOTIC THERAPY STRONGLY ENCOURAGED
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	LOW-RISK PATIENT: REPEAT PCT AFTER 1 - 2 DAYS / MODERATE-RISK PATIENT: REPEAT PCT AFTER 6 - 12 HOURS			REPEAT PCT EVERY 2 - 3 DAYS CONSIDER STOPPING ANTIBIOTICS EARLIER

SEE OVERLEAF FOR GUIDANCE ON CONTINUING OR STOPPING ANTIBIOTIC THERAPY

* LRTI: Lower Respiratory Tract Infection

VIDAS® B·R·A·H·M·S PCT™ supports the clinical management of sepsis, and procalcitonin cut-off thresholds are an aid to the clinical management of LRTI, but under no circumstances replace clinical judgment. Information on this document is given as a guideline only and is not intended to be exhaustive. It in no way binds bioMérieux S.A. to the diagnosis established or the treatment prescribed by the physician.

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Vidas B·R·A·H·M·S PCT

Procalcitonin-based algorithm for decision to CONTINUE or STOP ANTIBIOTICS for patients with LOW or MODERATE RISK LRTI*

Source: Schuetz P, et al. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med. 2011;171:1322-31.

> ⚠ **PCT results do not replace clinical assessment and judgment.**

LOW-RISK LRTI: Primary Care / Emergency
Low-acuity non-pneumonic infections (acute bronchitis, acute exacerbations of Chronic Obstructive Pulmonary Disease (COPD) or asthma)

MODERATE-RISK LRTI: Hospital / Emergency
Moderate-acuity pneumonic infections

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

LRTI PATIENT ON ANTIBIOTIC THERAPY

Repeat PCT test

PCT™ test result on follow-up (ng/mL)	<0.1	0.1 - <0.25	0.25 - <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 ENCOURAGED	CONTINUING ANTIBIOTIC THERAPY STRONGLY ENCOURAGED
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	LOW-RISK PATIENT: REPEAT PCT AFTER 1 - 2 DAYS MODERATE-RISK PATIENT: REPEAT PCT AFTER 6 - 12 HOURS		MODERATE-RISK PATIENT: REPEAT PCT EVERY 2 - 3 DAYS	IF PCT REMAINS HIGH, TREATMENT FAILURE LIKELY

⚠ OVER-RULING PCT ALGORITHM: LOW-RISK LRTI PATIENT
Consider use of antibiotics if patients are clinically unstable, have strong evidence of pneumonia, are at high risk (i.e. COPD, GOLD III/IV), or need hospitalisation.

⚠ OVER-RULING PCT ALGORITHM: MODERATE-RISK LRTI PATIENT
Consider alternative diagnosis or antibiotic treatment if patients are clinically unstable, are at high risk for adverse outcome (e.g. PSI classes IV-V, immunosuppression), have strong evidence of bacterial origin or need hospitalisation. Consider CONTINUATION of antibiotics if patients are clinically unstable.

* COPD: Chronic Obstructive Pulmonary Disease
GOLD: Global initiative for chronic Obstructive Lung Disease
LRTI: Lower Respiratory Tract Infection
PSI: Pneumonia Severity Index

Procalcitonin-based algorithm 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 and Schuetz P, et al. Arch Intern Med. 2012 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. Dellinger RP, et al. Crit Care Med 2013;41:580-637.

> ⚠ **PCT results do not replace clinical assessment and judgment.**

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	IF SEPSIS IS NOT SUSPECTED AFTER CLINICAL EVALUATION, CONSIDER ALTERNATIVE DIAGNOSIS	ANTIBIOTIC THERAPY ENCOURAGED	ANTIBIOTIC THERAPY STRONGLY ENCOURAGED	
Follow-up comments	CLINICAL RE-EVALUATION ADVISED		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

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VIDAS® B·R·A·H·M·S PCT™ supports the clinical management of sepsis, and procalcitonin cut-off thresholds are an aid to the clinical management of LRTI, but under no circumstances replace clinical judgment. Information on this document is given as a guideline only and is not intended to be exhaustive. It in no way binds bioMérieux S.A. to the diagnosis established or the treatment prescribed by the physician.

Procalcitonin-based algorithm 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 2010I and Schuetz P, et al. Arch Intern Med. 2012 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. Dellinger RP, et al. Crit Care Med 2013;41:580-637.

⚠ **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	CLINICAL RE-EVALUATION ADVISED	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

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▶▶▶ 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 *Staphyloccus aureus*
PCT	Procalcitonin
Pro-CT	Prohormone of calcitonin
PSI	Pneumonia severity index
SIRS	Systemic inflammatory response syndrome
TNF	Tumor necrosis factor
VAP	Ventilator-associated pneumonia