ALSO AVAILABLE:

- PCT booklets (testimonials and case studies in adult population and pediatric setting)
- PCT-based algorithm for antibiotic therapy guidance in LRTI/Sepsis

Other educational booklets are available. Consult your local bioMérieux representative.

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Geneva University Hospitals (HUG),
Geneva, Switzerland

and

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

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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.
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 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).
Plasma concentration

Time (hours)

0 1 2 6 12 24 48 72

IL-6
IL-10
TNF
PCT
CRP

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. PCT shows an interesting kinetic profile.

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. 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.

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.

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.
INFLAMMATORY HOST RESPONSE

Bacterial infection (e.g. Endotoxin)

Pro CT

CT-mRNA

Viral infection

Different tissues

Golgi apparatus

Constitutive Secretion

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


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

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.

Figure 3: PCT cut-off levels adapted to acuity.


**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.

**3A. LOW ACUITY**

<table>
<thead>
<tr>
<th>BACTERIAL INFECTION?</th>
<th>Bacterial infection is likely if PCT is &gt;0.25 and the clinical presentation is suggestive of infection</th>
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</thead>
<tbody>
<tr>
<td>VERY UNLIKELY</td>
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<th>PCT ng/mL</th>
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<th>HIGH ACUITY</th>
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**3B. HIGH ACUITY**

<table>
<thead>
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<th>BACTERIAL INFECTION?</th>
<th>Low risk of sepsis; other non-infectious diagnoses are more likely and should be considered</th>
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<tbody>
<tr>
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<th>PCT ng/mL</th>
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<td>&gt;10</td>
<td>HIGH ACUITY</td>
<td>HIGH ACUITY</td>
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</table>

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.

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.

For 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.

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

LOW ACUITY refers to patients with low risk of marked bacterial infection; other diagnoses should be considered.

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

HIGH ACUITY reflects the presence of sepsis or other severe conditions requiring intensive care.

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

**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.

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

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 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.
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)

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

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


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

Source: Thermo Fisher Scientific communication “Guide for the Clinical Use of Procalcitonin (PCT)”

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

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

---

*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).*
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:\(^\text{19}\):

**IN LOW-ACUITY PATIENTS WITH RESPIRATORY INFECTIONS:**
- a low PCT level identifies patients at lower risk for a bacterial etiology and CAP and thus low mortality;
- 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\(^\text{20-23}\).

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\(^\text{24}\). **Monitoring the change in PCT over time**, in conjunction with other laboratory findings and clinical assessments, helps assess the cumulative 28-day risk of mortality for patients with sepsis or septic shock who are admitted to the ICU.

The key findings of this major multi-site 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 \(\leq 80\%\) during the first four days following diagnosis of sepsis or septic shock, a 2-fold increased risk of death was observed, compared to those who experienced a decrease in PCT > 80%.
- The initial PCT level (\(\leq 2.0\) 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.

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 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\(^\text{17}\).
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.

The “BACH” trial (25) including 1,641 patients presenting to the ED with dyspnea found PCT helpful in such cases of high diagnostic uncertainty, 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 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 high CSF protein level and interpreted with clinical rules is a sensitive and specific marker to identify bacterial meningitis (26). 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 an elevated PCT concentration is associated with renal damage and is significantly higher in children with renal scars.

■ 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.

■ PREDICTION OF PNEUMOCOCCAL PNEUMONIA
Elevated PCT and CRP in combination with a positive pneumococcal urinary antigen are reliable predictors of pneumococcal pneumonia (29).
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) (31). Furthermore, in another 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 (32).

## 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). 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 algorithm in newborns suspected of Early Onset Neonatal Infections (EONI)(37).

This algorithm 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.

<table>
<thead>
<tr>
<th>AGE (hours)</th>
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<tr>
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<tr>
<td>42-48</td>
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</tbody>
</table>

Table 1: PCT levels in neonates

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.

Serum PCT levels at presentation have very good diagnostic accuracy (AUC=0.87) for the diagnosis of neonatal sepsis (34). The use of a PCT-guided algorithm can shorten antibiotic therapy in suspected neonatal early-onset sepsis (32).

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).
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.

![Figure 8: Antibiotic use in primary care with (red) and without (grey) PCT guidance.](image)


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).
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 23).

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

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 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). 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 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.

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)\(^9\).

In community-acquired pneumonia (CAP), monitoring the course of PCT helps shorten the duration of treatment. A PCT guided strategy therefore has important clinical and epidemiological implications: helping to prevent the selection of resistant bacteria and reducing the risk of cross-contamination, as well as decreasing treatment costs\(^{38}\).

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)\(^9\).

In community-acquired pneumonia (CAP), monitoring the course of PCT helps shorten the duration of treatment. A PCT guided strategy therefore has important clinical and epidemiological implications: helping to prevent the selection of resistant bacteria and reducing the risk of cross-contamination, as well as decreasing treatment costs\(^{38}\).
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 algorithms, 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 critically ill patients, a strong suspicion of severe bacterial infection with a PCT level above 2 ng/mL are diagnostic of sepsis with a high sensitivity and specificity, 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 12).

- 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 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.

### Table: Evaluation at time of admission

<table>
<thead>
<tr>
<th>PCT result (ng/mL)</th>
<th>&lt;0.25</th>
<th>0.25 - &lt;0.5</th>
<th>0.5 - &lt;1.0</th>
<th>≥1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation regarding use of Abx</td>
<td>STRONGLY ENCOURAGED</td>
<td>DISCOURAGED</td>
<td>ENCOURAGED</td>
<td>STRONGLY ENCOURAGED</td>
</tr>
<tr>
<td>Overruling the algorithm</td>
<td>Empirical therapy recommended in all patients with clinical suspicion of infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up/other comments</td>
<td>Consider alternative diagnosis; reassess patients' condition and recheck PCT level every 2 day</td>
<td>Reassess patients' condition and recheck PCT level every 2 day to consider stopping Abx</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table: Follow-up evaluation every 1 to 2 days

<table>
<thead>
<tr>
<th>PCT result (ng/mL)</th>
<th>&lt;0.25 or drop by &gt;90%</th>
<th>0.25 - &lt;0.5 or drop by ≥80%</th>
<th>0.5 and drop by &lt;80%</th>
<th>≥1.0 and PCT rise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation regarding use of Abx</td>
<td>STOPPING ABx STRONGLY ENCOURAGED</td>
<td>STOPPING ABx ENCOURAGED</td>
<td>CONTINUING ABx ENCOURAGED</td>
<td>CONTINUING ABx STRONGLY ENCOURAGED</td>
</tr>
<tr>
<td>Overruling the algorithm</td>
<td>Consider continuation of Abx if patients are clinically not stable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up/other comments</td>
<td>Clinical reevaluation as appropriate</td>
<td>Consider treatment to have failed if PCT level does not decrease adequately</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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).

**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 13) (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.**
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.

Figure 13: Comparison of PCT in patients with complicated (infection) and uncomplicated post-operative courses
IV

FREQUENTLY ASKED QUESTIONS

1 Is there an international standard for procalcitonin assays?

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

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

- **Non-specific elevations** of PCT levels in the absence of a bacterial infection can typically be seen in situations of massive stress, e.g. after severe trauma, cardiac shock or surgery. In these situations, PCT values are usually only moderately elevated and show a rapid decline in follow-up measurements.

- Conversely, **falsely low PCT levels**, typically seen during the early course or in localized infections (i.e. empyema), often show an increase in the follow-up measurements. In these cases, subtle increases of PCT may already point to an underlying infection. Therefore, **highly sensitive PCT assays are required**, as subtle changes of PCT at very low concentrations can be monitored, increasing the test’s sensitivity and therefore patient safety.

3 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.

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

**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.
Is PCT testing cost-effective?

An important consideration when using a new diagnostic test is the cost associated with the test with respect to the potential for producing other healthcare-related cost-savings.

Several studies have shown that PCT in the critical care setting (ICU) is cost-effective if used to guide antibiotic decisions due to the high antibiotic costs associated with critically ill patients (51, 52).

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.

Observational studies suggest PCT may improve diagnosis in immunosuppressed patients and PCT levels are not affected by corticosteroids.

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 (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.

Cost-effective diagnostic solutions can therefore contribute significantly to reducing the cost of sepsis.

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Observational studies suggest PCT may improve diagnosis in immunosuppressed patients and PCT levels are not affected by corticosteroids.
GUIDELINES AND 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 third edition of the Surviving Sepsis Campaign (SSC) Guidelines published in 2012 suggests “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). In 2015, the SSC Care Bundles were revised 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).

- The 2011 Brazilian Medical Association Guidelines for the treatment of sepsis and septic shock refer to the use of PCT-guided algorithms to guide and shorten antibiotic therapy duration in this population (63).

- Similarly, sepsis and emergency department guidelines in Sweden, the US, China, Spain and Ireland have also included PCT (64-67). 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). 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 (65). The 2014 Irish guidelines include PCT as an inflammatory marker in the diagnostic criteria for sepsis (67).

NEW DEFINITIONS FOR SEPSIS AND SEPTIC SHOCK


- 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 14).

Adult patients with suspected infection can be rapidly identified as more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria:

- respiratory rate of > 22/min,
- altered mental state,
- systolic blood pressure of < 100 mm Hg
Table 2: The SOFA Score: Sequential (Sepsis-Related) Organ Failure Assessment Score

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RESPIRATION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{PaO}_2/\text{FiO}_2), mmHg (kPa)</td>
<td>(\geq 400) (53.3)</td>
<td>&lt;400 (53.3)</td>
<td>&lt;300 (40)</td>
<td>&lt;200 (26.7) with respiratory support</td>
<td>&lt;100 (13.3) with respiratory support</td>
</tr>
<tr>
<td><strong>COAGULATION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets, (\times 10^3/\mu\text{L})</td>
<td>(\geq 150)</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td><strong>LIVER</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, mg/dL ((\mu\text{mol}/\text{L}))</td>
<td>&lt;1.2 (20)</td>
<td>1.2-1.9 (20-32)</td>
<td>2.0-5.9 (33-101)</td>
<td>6.0-11.9 (102-204)</td>
<td>&gt;12.0 (204)</td>
</tr>
<tr>
<td><strong>CARDIOVASCULAR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>MAP (\geq 70)</td>
<td>MAP &lt;70 mmHg</td>
<td>Dopamine &lt;5 or dobutamine (any dose)(^b)</td>
<td>Dopamine 5.1-15 or epinephrine (&lt;0.1) or norepinephrine (&lt;0.1)(^a)</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1(^a)</td>
</tr>
<tr>
<td><strong>CENTRAL NERVOUS SYSTEM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale score(^b)</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
</tr>
<tr>
<td><strong>RENAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL ((\mu\text{mol}/\text{L}))</td>
<td>&lt;1.2 (110)</td>
<td>1.2-1.9 (110-170)</td>
<td>2.0-3.4 (171-299)</td>
<td>3.5-4.9 (300-440)</td>
<td>&gt;5.0 (440)</td>
</tr>
<tr>
<td>Urine output, mL/d</td>
<td></td>
<td></td>
<td>&lt;500</td>
<td>&lt;200</td>
<td></td>
</tr>
</tbody>
</table>

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 \(\mu\text{g}/\text{kg}/\text{min}\) for at least 1 hour.
\(^b\) Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

---

Figure 14: Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock

PATIENT WITH SUSPECTED INFECTION

- \(q\text{SOFA} \geq 2\)? (see A)
  - NO
  - YES: Sepsis still suspected?
    - NO
    - YES: Assess for evidence of organ dysfunction

  - q\text{SOFA} \geq 2? (see B)
    - NO
    - YES: SOFA \geq 2? (see B)
      - NO
      - YES: SEPSIS

  - Despite adequate fluid resuscitation, 1. vasopressors required to maintain MAP \(\geq 65\) mm Hg AND 2. serum lactate level \(>2\) mmol/L?
    - NO
    - YES: SEPTIC SHOCK

- Monitor clinical condition; reevaluate for possible sepsis if clinically indicated

- A \(q\text{SOFA} Variables\)
  - 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.
Procalcitonin-based algorithm for decision to **START ANTIBIOTICS** for patients presenting with suspected **LOW** or **MODERATE RISK** LRTI*


**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**

1. **PERFORM CLINICAL ASSESSMENT**
2. **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**
  - **IF NO CLINICAL IMPROVEMENT, CLINICAL RE-EVALUATION ADVISED**

- **FOLLOW-UP COMMENTS**
  - **LOW-RISK PATIENT: REPEAT PCT AFTER 1 - 2 DAYS**
  - **MODERATE-RISK PATIENT: REPEAT PCT AFTER 6 - 12 HOURS**

- **REPEAT PCT TEST**

---

**SEE OVERLEAF FOR GUIDANCE ON CONTINUING OR STOPPING ANTIBIOTIC THERAPY**
Procalcitonin-based algorithm for decision to **CONTINUE** or **STOP ANTIBIOTICS** for patients with **LOW** or **MODERATE RISK LRTI**

**LRTI PATIENT ON ANTIBIOTIC THERAPY**

- **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
  - **CONTINUING ANTIBIOTIC THERAPY STRongly ENCouraged**

- **Follow-up comments**
  - **CLINICAL RE-EVALUATION ADVISED**
  - **OVER-RULING PCT ALGORITHM:**
    - **LOW-RISK LRTI PATIENT:** Consider use of antibiotics if patients are clinically unstable, have strong evidence of pneumonia or need hospitalisation.
  - **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.

- **PATIENT PRESENTING WITH CLINICAL SIGNS OF SEPSIS**

- **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**
  - **START EMPIRIC ANTIBIOTIC THERAPY IMMEDIATELY, IF SEPSIS IS STRONGLY SUSPECTED**

- **Follow-up comments**
  - **CLINICAL RE-EVALUATION ADVISED**
  - **OVER-RULING PCT ALGORITHM:**
    - **LOW-RISK LRTI PATIENT:** Consider use of antibiotics if patients are clinically unstable, have strong evidence of pneumonia or need hospitalisation.
  - **MODERATE-RISK LRTI PATIENT:** Consider alternative diagnosis or antibiotic treatment if patients are clinically unstable, are at high risk for severe outcome (e.g. PSI classes IV-V, immunosuppression, have strong evidence of bacterial origin or need hospitalisation).

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

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

- **PATIENT PRESENTING WITH CLINICAL SIGNS OF SEPSIS**

- **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**
  - **OVER-RULING PCT ALGORITHM:**
    - **LOW-RISK LRTI PATIENT:** Consider use of antibiotics if patients are clinically unstable, have strong evidence of pneumonia or need hospitalisation.
or STOP ANTIBIOTICS
1, 2, 3

INTENSIVE CARE UNITS
et al. Arch Intern Med. 2011

with recommendations to consider antibiotic treatment to maximize patient safety.2,3 Adapted from Bouadma L, et al. Lancet 20101 and Schuetz P, et al.


PCT test result on follow-up

=0.5 and PCT level by ≥80%*

CONTINUING ANTIBIOTIC THERAPY

0.25 of PCT level by >90%*

STopping ANTIBIOTIC THERAPY

0.25 <0.5 of PCT level by ≥80%*

CONTINUING ANTIBIOTIC THERAPY

≥1.0 and PCT level

CONTINUING ANTIBIOTIC THERAPY STRONGLY ENCOURAGED

STOPPING ANTIBIOTIC THERAPY STRONGLY ENCOURAGED

STOPPING ANTIBIOTIC THERAPY ENCOURAGED

CONTINUING ANTIBIOTIC THERAPY ENCOURAGED

CLINICAL RE-EVALUATION ADVISED

ONE OF TWO

IF PCT REMAINS HIGH

TREATMENT FAILURE LIKELY

STOPPING ANTIBIOTIC THERAPY

REPEATE PCT EVERY 1 - 2 DAYS

CONTINUE ANTIBIOTIC THERAPY

if clinical improvement

if clinical improvement

Follow-up comments

Repeat PCT test

IF PATIENT IS CLINICALLY UNSTABLE

CLINICAL RE-EVALUATION ADVISED

Decision to CONTINUE or STOP ANTIBIOTIC THERAPY

PCT test result on follow-up (ng/mL)

0.25 of PCT level by >90%*

CLINICAL RE-EVALUATION ADVISED

ONE OF TWO

CONTINUE ANTIBIOTIC THERAPY

StrengHTLY ENCOURAGED

STILL ANTIBIOTIC THERAPY ENCOURAGED

TREATMENT FAILURE LIKELY

CONTINUE ANTIBIOTIC THERAPY

Follow-up comments

Repeat PCT test

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

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

