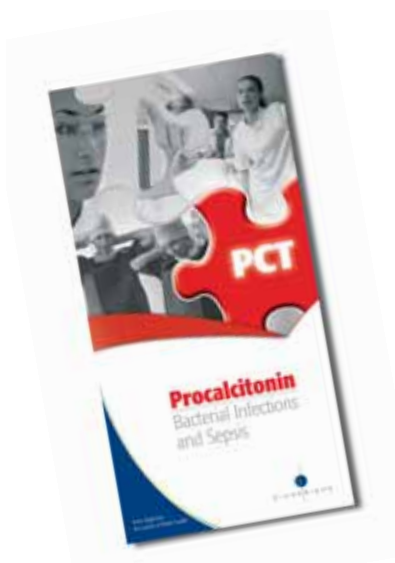


bioMérieux
Empowering Clinical Decisions
in the Management of Severe
Bacterial Infections

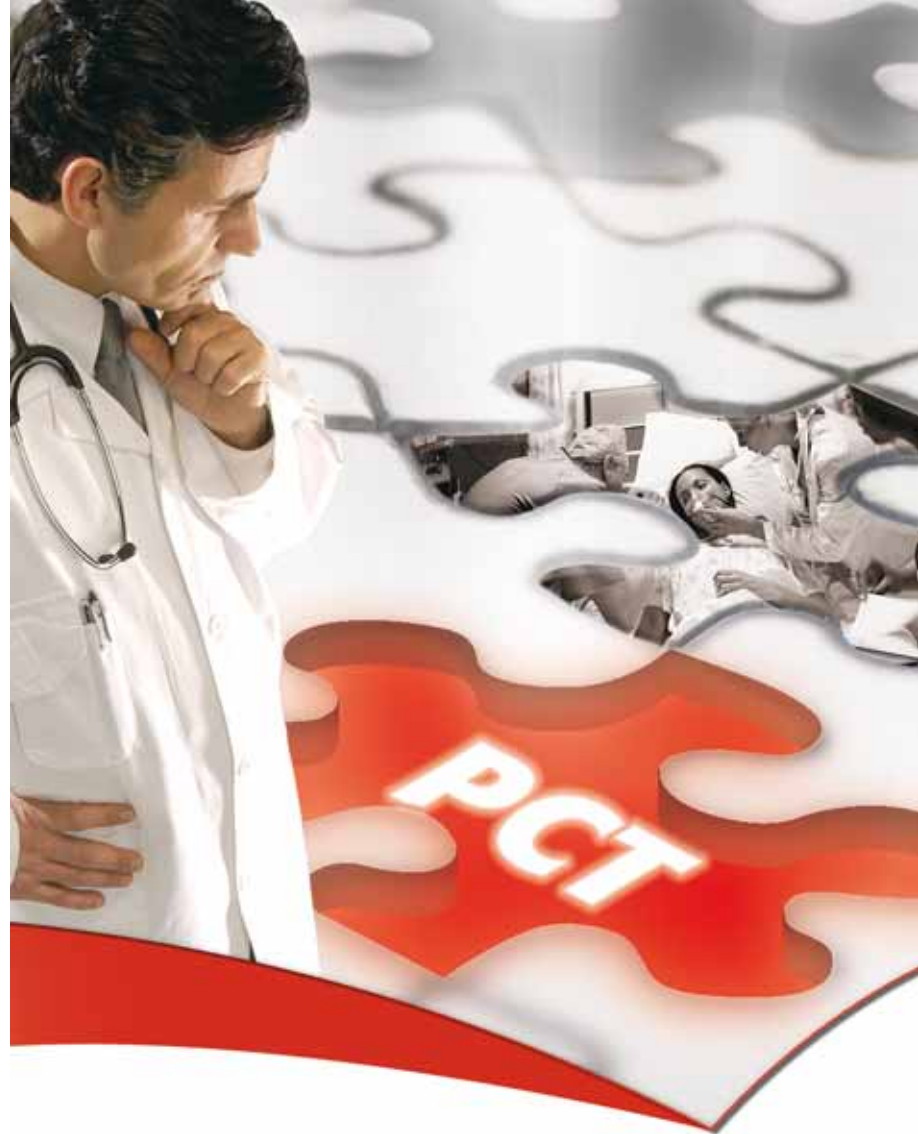


Also available:
Educational booklet on Procalcitonin providing an overview
of the main indications for this biomarker



bioMérieux S.A.
69280 Marcy l'Etoile
France
Tel. : 33 (0)4 78 87 20 00
Fax : 33 (0)4 78 87 20 90

www.biomerieux.com
www.biomerieux-diagnostics.com/procalcitonin



Procalcitonin

A useful biomarker in
the management of severe
bacterial infections

Clinicians' experience and case studies



**This booklet was created
with the kind participation of:**

- **Philipp Schuetz, MD.**
Emergency Dept., University Hospital,
Basel, Switzerland
- **Pierre Hausfater, MD., PhD.**
Emergency Dept., La Pitié-Salpêtrière Hospital, UMPC Univ Paris 06,
Paris, France
- **GianPaolo Castelli, MD.**
Intensive Care Dept., Carlo Poma Hospital,
Mantova, Italy
- **Prof. Corsino Rey, MD., PhD.**
Pediatric ICU Dept., Hospital Universitario Central De Asturias,
Oviedo, Spain
- **Prof. Chien-Chang Lee, MD.**
Emergency Dept., University Hospital,
Taipei, Taiwan
- **Devendra Amin, MD.**
Critical Care Dept., Morton Plant Hospital, Clearwater,
Florida, USA
- **Sebastian Ugarte, MD.**
Intensive Care Dept., Hospital del Salvador,
Santiago, Chile
- **Prof. Konrad Reinhart, MD.**
Intensive Care Dept., University Hospital,
Jena, Germany

**We are deeply grateful for their key contributions and
valuable discussion of the practical use of PCT in the Emergency
Department (ED) and Intensive Care Unit (ICU) settings.**

For list of abbreviations used, refer to end of booklet.



Emergency Care and Intensive Care physicians face many daily challenges including the rapid and accurate diagnosis and severity assessment of bacterial sepsis.

The use of biomarkers, such as **procalcitonin (PCT)**, provides a novel, complementary approach to the early diagnosis of infection and evaluation of therapeutic response. In most cases of infection, a true "gold standard" for diagnosis does not exist. However, the measurement of PCT, in a clearly defined setting, has been shown to significantly **improve diagnostic and prognostic certainty**, as well as **reducing the prescription and duration of antimicrobial therapy**.^{1,2}

This booklet contains a select number of testimonials and clinical case studies provided by practicing clinicians (ED, ICU, pediatric) from around the world on the use of PCT in their daily practice.

Their experience shows how PCT may provide **added value in the clinical decision-making process** by contributing to the early diagnosis, prognostic assessment, therapeutic management and antibiotic stewardship of bacterial infections.

Disclaimer

This document provides clinicians' experience and actual case studies regarding the practical use of PCT measurement and interpretation of results in the ED and ICU settings. However, this does not relieve the clinician of the obligation to verify the interpretation of the laboratory result based on their clinical knowledge to assess the clinical status of each individual patient and to decide on appropriate treatment.

Neither bioMérieux nor the contributing clinicians assume any liability for any injury and/or damage to persons or property arising from the information published. Liability claims regarding damage caused by the use of any information provided, including any information which is incomplete or incorrect, will therefore be rejected.



PCT

What is Procalcitonin ?

Structure and synthesis

Procalcitonin (PCT) is the precursor of calcitonin (CT) and is expressed by the CALC-1 gene on chromosome 11.

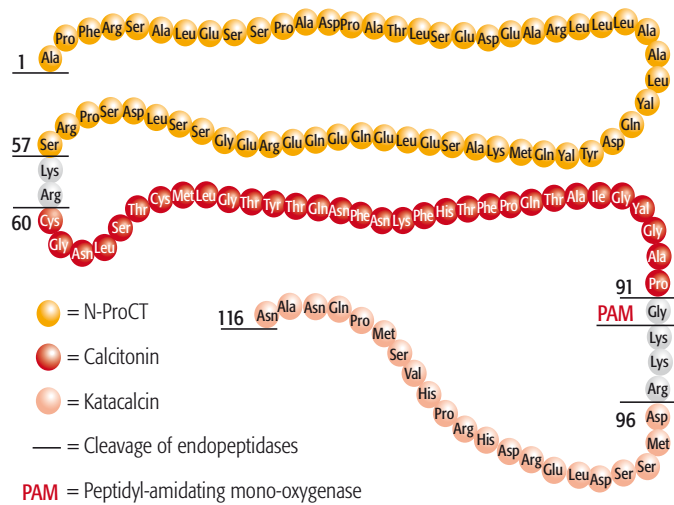


Figure 1: PCT structure adapted from Moullec *et al.*³

Whereas calcitonin is secreted exclusively by the C-cells of the thyroid after hormonal stimulation, PCT is produced by numerous cell types and organs after proinflammatory stimulation, especially when caused by bacterial infections.

In healthy individuals, PCT levels are found to be below 0.05 ng/mL, but can increase up to 1000 ng/mL in patients with severe sepsis or septic shock.

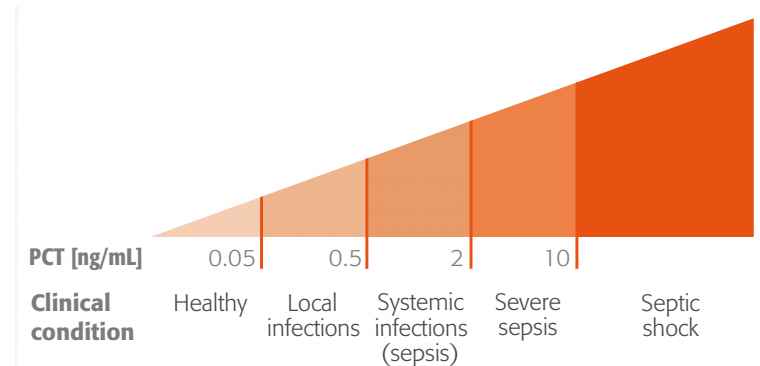


Figure 2: Adapted from Meisner *et al.*⁴

Increased PCT levels can be observed within 3 to 6 hours of an infectious challenge and rise with increasing severity of infection, making PCT an early and highly specific marker for severe systemic bacterial infection and sepsis.^{5,6}

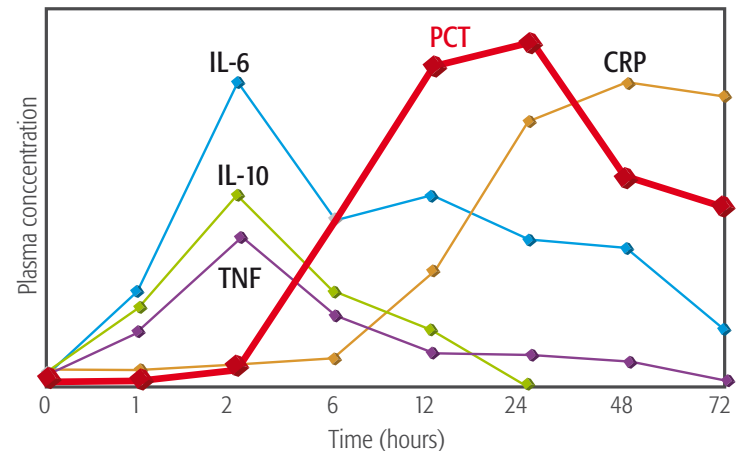


Figure 3: Adapted from Meisner *et al.*⁷

PCT returns to normal values of <0.05 ng/mL as the severe bacterial infection resolves, with a half life of 24 hours.⁷



Dr. Philipp SCHUETZ

Emergency Department
University Hospital
Basel, Switzerland

SUPPORT DIAGNOSIS OF SEPSIS AND ANTIBIOTIC GUIDANCE IN LRTI

PCT is the only biomarker that has good evidence that you can safely reduce antibiotics in LRTI.

How do you use a PCT test in your daily practice in ED ?

We use it in patients on admission to the ED presenting with suspicion of lower respiratory tract infections (LRTI). According to the clinical picture, the severity of disease, the underlying clinical diagnosis (chronic obstructive pulmonary disease (COPD), bronchitis or pneumonia) and the PCT level, we decide to give antibiotics or not. If antibiotics are started, PCT is re-measured after 3, 5 and 7 days so that treatment can be stopped early. We also use PCT for monitoring antibiotic therapy during severe sepsis.

Has PCT improved your diagnostic accuracy ?

Yes, diagnostic accuracy has improved due to the better specificity of PCT compared to other infection markers. Increased C-reactive protein (CRP) levels, for instance, are less specific and occur in both viral and bacterial disease.

PCT also gives us reassurance for our clinical work and provides another margin of safety to rule out severe bacterial infections, and decide when to start and stop antibiotic treatment.

What are the clinical cut-off levels your ED uses for PCT for sepsis diagnosis in the ED setting ?

In Basel and other Swiss hospitals, we use emergency algorithms that include PCT measurements.

We don't use strict PCT cut offs, but rather cut-off ranges, because they are more physiological and the biology of infections is not black or white. We usually only give antibiotics in patients with PCT values of <0.1 ng/mL if they are high-risk patients with most severe community-acquired pneumonia (CAP) or COPD (see algorithm opposite for over-riding rules). Normally we start or continue antibiotics in LRTI if PCT is >0.25 ng/mL and in severe sepsis in the ICU if it is >0.5 ng/mL (see algorithm below). It is important to re-measure PCT in all cases where antibiotics are withheld and the patient is not improving.

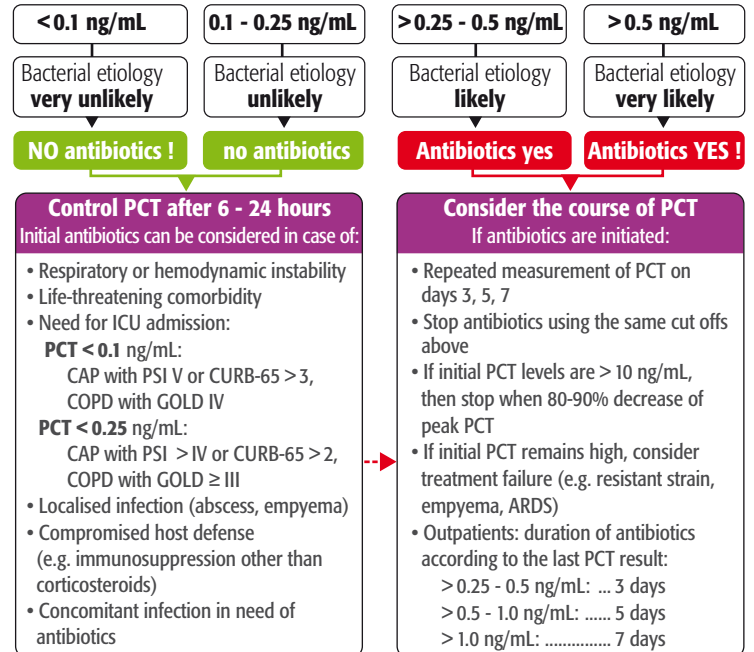


What are the cut-offs levels your ED uses for LRTI diagnosis and antibiotic stewardship ?

We use the clinical algorithm and cut-offs given in all of our intervention studies: proRESP, proCAP, etc (see below).^{8,9,10,11}

PCT-guided antibiotic treatment in the Emergency Department

Algorithm adapted from Schuetz P. et al.¹²



CAP: Community-Acquired Pneumonia

PSI: Pneumonia Severity Index

CURB-65: Scoring system for severity of pneumonia based on Confusion, serum Urea, Respiratory rate, Blood pressure, age >65

COPD: Chronic Obstructive Pulmonary Disease

GOLD: Scoring system for Chronic Obstructive Lung Disease

ARDS: Acute Respiratory Distress Syndrome

NO antibiotics !: antibiotic therapy STRONGLY DISCOURAGED

no antibiotics: antibiotic therapy discouraged

Antibiotics yes: antibiotic therapy recommended

Antibiotics YES !: antibiotic therapy STRONGLY RECOMMENDED

Have you been able to demonstrate the benefits of a PCT result ?

We have a lot of cases demonstrating PCT benefits included in randomized-controlled trials. We have just recently finished a multicenter trial including 6 major hospitals in Northern Switzerland and over 1,350 patients with LRTI.¹²



Dr. Pierre HAUSFATER, PhD.

Emergency Department
La Pitié-Salpêtrière Hospital
UMPC Univ Paris 06,
Paris, France

Emergency
Department

SUPPORT DIAGNOSIS AND PROGNOSIS OF SEVERE BACTERIAL INFECTION

Today, PCT is easily the best and most specific biomarker for severe bacterial infections, way ahead of CRP... ”

How is a PCT test used in your Emergency Department ?

In our Emergency Department, procalcitonin has two main applications:

- **Diagnosis** - in cases of suspected bacterial infection with fever but no focus of infection.
- **Prognosis** - in cases of sepsis to assess the severity of infection.

What cut-offs do you use ?

For diagnosis:

- We use a PCT cut-off of <0.25 ng/mL in cases of suspected community-acquired pneumonia (CAP) or acute exacerbation of chronic obstructive pulmonary disease (COPD) and to exclude "pseudo-flu-like" syndromes in cases of fever without infectious origin.
This supports the decision NOT to start antibiotic therapy.
- The exception is in immunocompromized patients where the cut-off used is 0.1 ng/mL.

For prognosis:

- A cut-off of >5 ng/mL is used for severity assessment.
- We also keep a patient under medical surveillance for 24 hours and/or orientate the patient to the intensive care unit if PCT >5 ng/mL and severe sepsis criteria are present.

How has PCT improved your diagnostic accuracy ?

PCT testing has helped us to refine our diagnostic judgement and improve our clinical accuracy in the following contexts:

- **Lower respiratory tract infections (LRTI)** based on the negative predictive value (NPV) of PCT. In this context, a negative PCT result (<0.25 ng/mL) argues for not introducing antibiotics.
- **Acute exacerbation of COPD:** PCT helps decide whether or not to prescribe antibiotics.
- **Pneumonia:** if imaging is not conclusive, PCT helps confirm infectious or non-infectious origin of respiratory symptoms.

How is PCT better than other inflammatory biomarkers, such as C-reactive protein (CRP) ?

PCT can give an indication of prognosis, since it is closely correlated to severity, which is not the case for CRP.

Any tips based on your experience in routine PCT testing ?

Yes ! You may obtain false negative results. You need to be careful about testing PCT too soon after the onset of symptoms, especially in patients brought to the ED by emergency services. Also, consider if the patient has been prescribed antibiotics by their general practitioner. Finally, false negative results can also be obtained in patients with a localized intra-abdominal infectious focus.

PCT: indicator of prognosis of infection in ED

19 year old male returning from a visit to Mali (Central Africa) presents to the Emergency Department with: Fever, headaches, abdominal pain but no diarrhoea. No underlying disease.

Triage results

- Blood pressure: 115/70
- Heart rate: 70/min
- Temp: 40°C
- Clinical examination: Non-purulent cutaneous excoriations (scratches or insect bites).
- No obvious infectious focus.



First results of investigations

- WBC: 15,500/μL (9,000 polynuclear neutrophils)
- CRP: 222 mg/L
- Chest X-ray: normal
- Abdominal echography: normal
- Lumbar puncture: normal
- Malaria test: negative
- Urinalysis: negative
- Kept in the emergency unit for observation.
- Plans to transfer patient next day to Infectious Disease (ID) Dept.

PCT test performed: 168 ng/mL



Next day checked vital signs

- Blood pressure: 85/60 mmHg
- Heart rate: 80/min
- Cancelled transfer to ID Dept.
- Start fluid resuscitation & antibiotic therapy.



Transfer to ICU for severe sepsis

- 4 days in Intensive Care.
- Blood culture positive results for *Streptococcus pyogenes*.
- Final diagnosis: severe sepsis of cutaneous origin.

The man was discharged in a good condition.

Conclusion

High PCT test result supports unfavorable prognosis of severe sepsis, leading to immediate transfer to ICU and initiation of sepsis resuscitation.

PCT: diagnosis and monitoring of bacterial infection in severe trauma

**42 year old male patient
Hospitalized in intensive care for severe trauma with fractures and crush syndrome**

On admission:

- Simplified acute physiology score (SAPS) II: 57
- Therapeutic intervention scoring system (TISS): 50
- WBC: 21,000/μL
- Glasgow coma scale (GCS): 9 (on 5th day, GCS: 15)



- Endotracheal intubation and mechanical ventilation.
- Central venous catheter, artery and urinary catheter, thoracic and naso-gastric tube insertion.
- After 48 hours, extracorporeal dialysis and evolution to anuria on 5th day.
- Microbiology cultures performed daily.

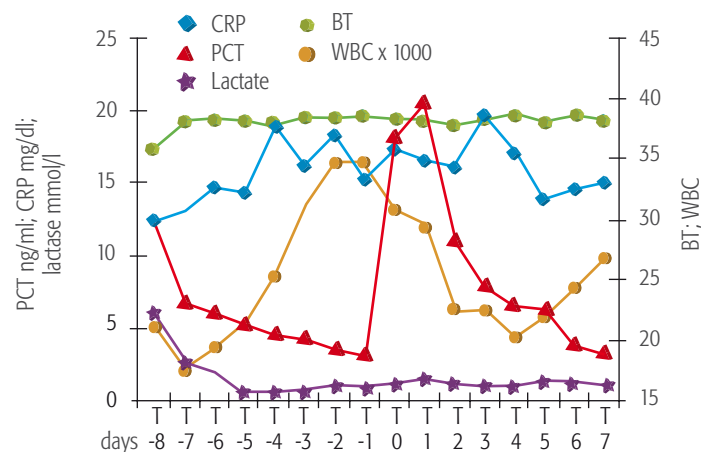


At Time 0 (after 8 days of ICU stay)

- Bloodstream infection develops from coagulase-negative *Staphylococcus*.

The patient was discharged after 35 days of ICU stay.

Daily evolution of parameters
PCT, CRP, WBC, lactate, BT (max. body temperature).



Conclusion

PCT was the best biomarker for diagnosis and monitoring of sepsis occurring 8 days after admission of trauma patient to ICU. Due to a peak PCT value and consequent decrease, it clearly shows the efficiency of the treatment course.



Dr. GianPaolo CASTELLI

Intensive Care Department,
Carlo Poma Hospital
Mantova, Italy

SUPPORT DIAGNOSIS AND PROGNOSIS OF SEVERE BACTERIAL INFECTION

We no longer test "in the dark"”

When do you use a PCT test in your daily practice ?

Our hospital lab has been testing PCT since 1999. This has given us experience with PCT in different patient groups and selected pathologies at various times during hospitalization.^{13, 14, 15}

Our objectives when testing PCT for critical patients are:

- discriminate between viral and bacterial sepsis (e.g. meningitis),
- support a clinical diagnosis of sepsis whilst waiting for a positive microbiology culture result,
- support a clinical diagnosis of organ failure (severe sepsis, septic shock), and monitor the effectiveness of the initiated therapy,
- rapidly discriminate systemic inflammatory response syndrome (SIRS) due to sepsis from other types of SIRS, e.g. trauma, post-operative, pancreatitis, acute respiratory distress syndrome (ARDS), and monitor the evolution of SIRS,
- on admission of patients with severe trauma, for potential assessment of prognosis of sepsis,
- monitor the evolution of the septic episode on the basis of the initiated therapy.

We use PCT as a general alarm in that it signals "attention" - something is not working !

How often ?

On a daily basis.

Single test results can be very useful for screening a patient presenting to the ED to exclude or to confirm a sepsis.

It is also very useful to test PCT daily to assess the clinical course of the ICU patient. The kinetics over time provide useful information for improved patient management.

What are the cut-offs you use ?

In the ICU, we don't use standardized cut-off values to diagnose sepsis.

We know that increasing values of PCT correspond to increasing disease severity and potential organ dysfunction.

In the absence of national or hospital-based guidelines, my department tests PCT daily in selected patients and assesses the kinetics i.e. the ratio between days.

A ratio of > 1.0 indicates we should search for other causes of the increase in PCT and that we should check that antibiotic therapy is adapted.

How is PCT better than other inflammatory biomarkers ?

PCT can be detected in the bloodstream after just 3 hours with a peak at 12 hours. This rapid increase and long half life (around 22 hours) means that it can be tested daily. Other markers (IL-6, IL-10, TNF α) have a shorter half-life, so multiple testing in one day is needed to observe the kinetics. This PCT dynamic is very useful when suspecting complications related to SIRS.

Why would you recommend PCT to other clinicians ?

I recommend PCT in the critical patient, together with careful and constant clinical evaluations.

Certainly PCT is not the perfect biomarker in that it lacks absolute specificity, but at the moment, I consider it to be the best biomarker available. WBC counts, body temperature, respiratory rate, hypotension and elevated lactate are not always enough to discriminate SIRS from sepsis, particularly in ICU patients.



Prof. Corsino REY, M.D., PhD.

Pediatric Intensive Care Unit,
Central De Asturias University Hospital
Oviedo, Spain

USING PCT VALUES TO OPTIMIZE CLINICAL MANAGEMENT

Useful biomarker to optimize diagnosis of pediatric sepsis and reduce antibiotic prescription

How do you use PCT in your daily practice ?

In our Pediatric Intensive Care Unit, we use PCT if there is a clinical suspicion of infection, systemic inflammatory response syndrome (SIRS), sepsis or septic shock. We test PCT every 24 hours to follow a patient's clinical evolution.

What are the applications ?

- Optimize diagnosis of infection, sepsis & septic shock.
- Decide to start antibiotic therapy or not.
- Decide to change treatment if PCT levels increase persistently.
- Assist decision to stop antibiotic therapy.

What PCT cut-offs do you use in your Pediatric ICU ?

Cut-off ranges are clearly dependent on the clinical context of the patient. However, after several years of investigation of PCT, we have developed our own guidelines. Tables 1 and 2 below and opposite show how we use both absolute and dynamic PCT values in our Pediatric ICU.

Table 1. Utility of PCT values for the clinical management of critically ill children.

PCT Absolute Value (ng/mL)	<0.1 ng/mL	0.1 – 0.25 ng/mL	>0.25 – 0.5 ng/mL	>0.5 – 1.0 ng/mL	>1.0 – 5.0 ng/mL	>5.0 - 100 ng/mL	>100 ng/mL
Clinical Interpretation	Normal value. Infection NOT LIKELY	- Infection NOT LIKELY. - Local bacterial infection is possible	- Infection LIKELY ⁽¹⁾ - Local bacterial infection is possible	- Infection LIKELY ⁽¹⁾	- Sepsis LIKELY ⁽¹⁾	- Severe bacterial sepsis or septic shock ⁽¹⁾	Septic Shock ⁽¹⁾ HIGH RISK of mortality
Retesting PCT		Caution: PCT may have been tested too early. Control PCT after 6-24 h.	Control PCT after 6-24 h.	Daily PCT measurement recommended ⁽²⁾	Daily PCT measurement recommended ⁽²⁾	Daily PCT measurement recommended ⁽²⁾	Daily PCT measurement recommended ⁽²⁾

PCT can increase in non-infectious Systemic Inflammatory Response Syndrome (see conditions below).

Footnotes
(1) Other PCT inducing conditions include:

- Severe trauma
- Major surgical interventions
- Prolonged cardiogenic shock
- Severe burns
- Treatment with OKT3 antibodies
- Invasive fungal infections
- *Plasmodium falciparum* (malaria)
- Prolonged severe organ perfusion anomaly
- Drugs stimulating release of pro-inflammatory cytokines
- Small cell lung cancer
- Medullary C-Cell carcinoma of thyroid

Has PCT testing changed your daily practice ?

PCT testing makes it possible to diagnose infection and sepsis earlier. Now I also use less antibiotics, and can better control patient evolution using PCT dynamics.

How has PCT improved your diagnostic accuracy ?

PCT contributes to optimized diagnosis of sepsis and infection, etiologic diagnosis of shock, and improved classification of SIRS.

How is PCT better than other inflammatory markers ?

Both PCT kinetics and negative predictive value (NPV) are better than other markers.

Table 2.

PCT DYNAMIC VALUE	CLINICAL INTERPRETATION
Persistently high or increasing	→ Poor evolution. Reconsider therapy.
Decreasing values (by half daily)	→ Good evolution. Maintain therapy.

Cut-off ranges are dependent on clinical context of the patient and must be adapted accordingly.

(2) Search for source of infection, and evaluate risk of developing organ dysfunction and response to therapy. Guide antibiotic treatment duration.

Utility of PCT dynamics to monitor clinical evolution in pediatric patients

1 year old boy

Presented to ED with high fever

Hospitalized for further examinations

Developed petequial rash

Transferred to Pediatric Intensive Care Unit (PICU)

with suspicion of meningococcal sepsis

At PICU admission (Figure 1):

- Tachycardia
- Normal blood pressure
- Decreased peripheral perfusion
- PCT levels: 50 ng/mL
- CRP levels: 50 mg/dL
- Lactate: 5 mmol/L



3rd generation cephalosporin, isotonic saline and continuous perfusion of dopamine started.



Over next 36 hours

PCT levels were higher than 500 ng/mL

- Clinical evolution was negative
- Mechanical ventilation started
- Continuous perfusion of adrenaline, amiodarone and furosemide



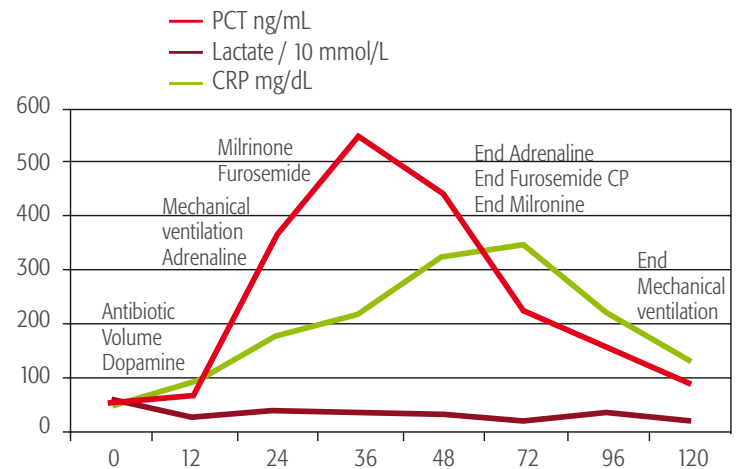
12 hours later

• PCT levels started to decrease – approximately by half every 24 hours

- CRP levels followed same trend as PCT but some hours late
- Lactate levels remained at around 2 mmol/L throughout
- Clinical evolution was favorable.
- Therapy progressively discontinued.
- Progressive analytical normalization observed.
- Meningococcus was isolated in a blood culture on the second day of evolution.

The infant was discharged after 8 days in PICU without any sequelae.

Figure 1. Blood levels of Procalcitonin (PCT), C-reactive Protein (CRP) and Lactate in a case of meningococcal septic shock



Conclusions

- PCT is a useful marker not only of sepsis but also of severity of illness. We have demonstrated PCT increases according to disease severity from sepsis to septic shock.¹⁶
- If PCT levels are increasing, as in the first 36 hours of our case, evolution is bad.
- The meningococcal infection was controlled by antibiotics, but the septic shock was not controlled, and PCT increased rapidly necessitating a therapeutic change.
- Following optimization of septic shock treatment, PCT levels decreased progressively indicating treatment was correct.
- Treatment based on daily PCT level changes may be initiated hours or days before the occurrence of clinical complications.¹⁷

Prof. Chien-Chang LEE, M.D.

Assistant Professor in Emergency Medicine,
College of Medicine, National Taiwan University
Taipei, Taiwan

SUPPORT IN DIAGNOSIS, MONITORING AND THERAPEUTIC GUIDANCE

*Better to light a candle - than
curse darkness* ”

How do you use a PCT test in your daily practice ?

- **In the ED** - to support differentiation between bacterial and viral Infection
- **In the ICU** - for prognosis and monitoring: assess evolution to severe sepsis
- **In Division of Allergy & Rheumatology** - to differentiate bacterial, allergic and autoimmune disease infections

We test for PCT when clinical symptoms, WBC and CRP are not specific enough or symptoms are unlikely.

What are the different applications ?

We use PCT to support diagnosis, prognosis and antibiotic guidance in a wide variety of clinical applications in both adults and pediatrics including:

- Sepsis
- Lower respiratory tract infections
- Pancreatitis
- Febrile neutropenia
- Meningitis, peritonitis, pyelonephritis

What are the cut-offs you use ?

We use the cut-offs recommended in the publication by Lee *et al.*¹⁸ At a cut-off of 0.5 ng/mL, PCT has a high sensitivity for predicting early (5-day) or late (6- to 30-day) mortality in the ED. On the other hand, the clinical MEDS score (Mortality in Emergency Department Sepsis) has a high specificity and, therefore, we recommend to combine PCT testing and the MEDS score to enhance the accuracy for predicting a worse evolution.

Has it changed the way you practice medicine ?

- **In the ED**, we use the PCT cut-offs proposed by Schuetz *et al.*¹² in the proHOSP study for the guidance of antibiotic therapy in patients with suspicion of chronic obstructive pulmonary disease (COPD), bronchitis and asthma cases.
- **In the ICU**, we use PCT serum levels to determine the patient's response to antibiotic treatment effectiveness.

CASE STUDY

PCT: guidance for initiation of antibiotic therapy in case of meningitis

54 year old male presenting with headache
Anterior communicating artery aneurysm

Post-operative day 7:

- Fever
- WBC: 13,200/ μ L
- Serum CRP: 118 mg/L
- **Serum PCT: <0.05 ng/mL**
- CSF: - glucose: 112 mg/dL
- protein: 45 mg/dL
- WBC: 3/ μ L
- RBC: 2/ μ L
- Gram stain: negative

Consider 1st antibiotic dose before CSF data available ?

- CSF culture: no growth.
- Sputum culture: mixed flora.
- Not favoring CNS infection so no antibiotics given.

Two weeks after operation:

Patient presents again in hospital
No fever
Headache, neck stiffness

- WBC: 9,600/ μ L
- Serum CRP: 14 mg/L
- **Serum PCT: 16.7 ng/mL**
- CSF: - glucose: 5 mg/dL
- protein: >500 mg/dL
- WBC: 224/ μ L (N/L:75/25)
- RBC: 3/ μ L
- Gram stain: negative

Consider 1st antibiotic dose before CSF data available ?

- Start antibiotics.
- CSF Culture: positive for methicillin-resistant *S. aureus*.

Patient improved.

Conclusion

High PCT test result supports decision to start antibiotic therapy when microbiological results are not yet available.



Dr. Devendra AMIN

Medical Director of Critical Care Services, Morton Plant Hospital, Clearwater.
Assistant Professor of Medicine, Department of Family Practice,
University of South Florida at Morton Plant Hospital
Morton Plant Mease Health Care - Clearwater, Florida, USA

DIAGNOSIS, MONITORING AND TREATMENT OF PNEUMONIA AND SEPSIS

PCT fine-tunes what we already do and can lead to fewer antibiotic days

How do you use a PCT result in your daily practice ?

We use it for new patient evaluation in the ED to help diagnose ambiguous or overlapping situations. PCT is also helpful in cases of symptom overlap between pneumonia and congestive heart failure. It provides a strong positive predictive value if high and is a good negative predictor if the level is normal.

When, and how often do you use a PCT result ?

- We measure PCT levels three times in the first 12 hours in patients suspected of having a potentially severe bacterial infection, when it is not clinically obvious.
- A rising level confirms the presence of a bacterial infection given the right clinical circumstances. Once the patient starts improving, we use it every other day, comparing the levels to the peak level. In some situations, it can help guide when to stop antibiotics.

How has a procalcitonin test changed your practice ?

- It's another test that helps confirm our patients are improving. For example, patients with pneumonia or sepsis often have a continuation of fever two to three days after antibiotic treatment has been started. This could suggest antibiotic failure and a possible need to change antibiotics.
- With this test, we can see PCT levels declining even though fever can continue for a few more days. This tells us we're on the right track and that the infection is responding to therapy. Hence, there is no need to change antibiotics. It's very nice not to have to second guess yourself on antibiotic usage.

What are the applications ?

Primarily pneumonia and sepsis. However, we also see that chronic obstructive pulmonary disease (COPD)/asthmatic/bronchitis patients are often given too many antibiotics. We can now de-escalate antibiotic treatment on these patients much faster with the help of PCT.

We will still begin treatment of these patients with antibiotics when there is a suspicion and PCT is low, because the levels can rise rapidly in the first 6 - 24 hours. Given the dynamic nature of PCT levels, we can make rapid decisions about the relevance and continuation of treatment within hours.

What cut-offs do you use ?

<0.05 - 0.1 ng/mL	Normal	
>0.1 - 0.25 ng/mL	Bacterial infection unlikely	
>0.25 - 0.5 ng/mL	Bacterial infection possible	Advise to start antibiotics
>0.5 ng/mL	Bacterial infection highly likely	Strongly suggest to start antibiotics

Do you have national guidelines that you follow ?

There are no national guidelines in the U.S. The hospital guideline we have developed requires patients to be tested immediately upon presentation, and then again at hours six and twelve.

If the PCT level is flat (below 0.05 ng/mL), we stop testing. If the PCT level is rising, we'll continue to test every other day. Typically, the PCT level surges within the first 12 hours, despite starting appropriate antibiotics, and then responds to therapy.

How is PCT better than other inflammatory biomarkers ?

- I think PCT is better than CRP and WBC because it is much more reactive and dynamic. PCT levels also respond quickly to treatment.
- We had a great curve on a recent patient with severe pancreatitis. The PCT levels went up quickly in the patient, then dropped within 48 hours almost to normal levels, while both CRP and WBC remained high for several more days. There were no signs of infection by CT scan. This allowed us to stop antibiotics quickly as there were no other signs of infection.

Can you provide a clinical example of PCT use ?

Recently, we had two post-operative patients in the cardiothoracic intensive care unit with post-operative fevers.

- In the patient with fever and cough, the PCT level went up with the febrile illness to about 4 - 5 ng/mL. The chest X-ray (CXR) had changes of "infiltrate", possibly atelectasis or pneumonia. The levels came back down to close to baseline by Day 5, allowing antibiotics to be stopped on Day 6. Cultures (blood, sputum and urine) were all negative.
- In the other patient, the PCT level did not rise significantly with fever, despite similar CXR changes. Serial PCT levels did not rise above 0.5- 1.0 ng/mL, and antibiotics were de-escalated at 48 hours to treat for probable bronchitis.

Without PCT guidance, both patients would probably have been given full antibiotic treatment for 7-10 days.



Dr. Sebastian UGARTE

Intensive Care Department
Hospital del Salvador
Santiago, Chile

DIAGNOSIS AND MONITORING OF SEPSIS

Increased precision for diagnosis of clinically important bacterial infections

When do you use PCT testing in your daily practice ?

I use PCT to assess critical patients with clinical suspicion of bacterial infection, with inflammatory response, or systemic inflammatory response syndrome (SIRS). I test PCT levels in all patients in our Critical Patients Unit to monitor for the presence of bacterial infection, assess whether an infection is evolving favorable or not, and detect super-infection in a patient hospitalized for another cause.

How has PCT changed your daily practice in the Critical Care Unit ?

- **In the critical patient**, the focus of bacterial infection is usually ventilator-associated pneumonia (VAP), which is particularly complex to diagnose. In this context, PCT determination can be used to confirm the clinical suspicion of bacterial infection.
- **In neurological patients**, where a fever syndrome may be of central origin, a PCT result can help the clinician to refine their focus and decide whether to start antibiotic therapy.

How has PCT improved your diagnostic accuracy ?

In the daily assessment of critically ill patients with suspected infection, PCT can tip the balance as to whether or not to start antibiotic therapy, when clinical background and other laboratory exams cannot provide a sufficient level of security.

What are the cut-offs you use ?

Depending on the objective and the clinical context, different cut-offs can be used. Generally, values under 0.25 ng/mL make it possible to rule out bacterial infection. Values over 0.5 ng/mL are probably due to bacterial infection, and in doubtful cases, the evolution of PCT kinetics reinforces this probability. Serial PCT measurements are useful to forecast prognosis and the presence of a complication in a critical patient.

How is PCT better than other inflammatory biomarkers ?

There is enough evidence in the literature that PCT is more accurate than leukocyte count, speed of erythrocyte sedimentation or CRP as a predictor of a relevant bacterial infection and the diagnosis of pneumonia and other severe infections in critical patients.

Can you provide a clinical example of PCT use ?

Every day, we have new cases and examples which document PCT in clinical practice.

- The latest example was a male patient with chronic obstructive pulmonary disease (COPD) associated with mechanical ventilation and who was about to be withdrawn from the ventilator. This patient had resisted intermittent T-tube periods previously and then his tolerance to T-tube ventilation started to decrease.
- The hemogram showed discrete leukocytosis and the clinical picture was not sufficient for diagnosis. It was suspected that a bacterial infection could be complicating his evolution and a PCT test was carried out.
- Two PCT determinations resulted as normal, so the patient did not receive any antibiotic treatment. He required withdrawal from pleural drainage due to surgery and suitable analgesic handling. Withdrawal from the mechanical ventilator was successful and the patient avoided unnecessary antibiotic treatment. The radiography and computer-run tomography ruled out any presence of new infiltrators or collections related to surgery.

Normal PCT results enabled the physician to rule out the need for antibiotic treatment.

REFERENCES

1. Christ-Crain M, Müller B. Procalcitonin in bacterial infections – hype, hope or more or less? *Swiss Med Wkly* 2005; 135: 451-460.
2. Schuetz P, Christ-Crain M, Müller B. Procalcitonin and other biomarkers for the assessment of disease severity and guidance of treatment in bacterial infections. *Adv Sepsis* 2008; 6: 82-89.
3. Moullec J.M, Jullienne A, Chenais J, Lasmoles F, Guliana J.M, Milhaud G, Moukhtar M.S. The complete sequence of human procalcitonin. *FEBS Lett* 1984; 167: 93-97.
4. Meisner M, Rotgeri A, Brunkhorst F.M. A semi-quantitative point-of-care test for the measurement of procalcitonin. *J Lab Med* 2000; 24: 076-085.
5. Harbarth S, Holekova K, Froidevaux C, Pittet D, Ricou B, Grau GE, Vadas L, Pugin J. Geneva Sepsis Network. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. *Am J Respir Crit Care Med*. 2001; 164: 396-402.
6. Müller B, Becker KL, Schädinger H, Rickenbacher PR, Huber PR, Zimmerli W, Ritz R. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med*. 2000; 28: 977-983.
7. Meisner M. Procalcitonin: Experience with a new diagnostic tool for bacterial infection and systemic inflammation. *J Lab Med* 1999; 23: 263-272.
8. Christ-Crain M, Jaccard-Stolz, Bingisser R, Gencay MM, Huber PR, Tamm M, Müller B. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004; 363: 600-607 (ProRESP study).
9. Christ-Crain M, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M, Müller B. Procalcitonin-guidance of antibiotic therapy in community-acquired pneumonia. *Am J Respir Crit Care Med* 2006; 174: 84-93 (ProCAP study).
10. Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Müller C, Huber P, Müller B, Tamm M. Antibiotic treatment of exacerbations of COPD: A randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest* 2007; 131: 9-19 (ProCOLD study).
11. Briel M, Schuetz P, Müller B, Young J, Schild U, Nusbaumer C, Périat P, Bucher HC, Christ-Crain M. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. *Arch Intern Med*. 2008; 168: 2000-2007 (PARTI study).
12. Schuetz P, Christ-Crain M, Wolbers M, Schild U, Thomann R, Falconnier C, Widmer I, Neidert S, Blum CA, Schönenberger R, Henzen C, Bregenzler T, Hoess C, Krause M, Bucher HC, Zimmerli W, Müller B. Procalcitonin-guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections: a prospective, multicenter, randomized controlled trial. *BMC Health Serv Res* 2007; 7: 102 (ProHOSP study).
13. Castelli GP, Pognani C, Meisner M, Stuaní A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. *Crit Care* 2004; 8(4): R234-42.
14. Castelli GP, Pognani C, Cita M, Sgarbi L, Paladini R. Procalcitonin, C-reactive protein, white blood cells and SOFA score in ICU: diagnosis and monitoring of sepsis. *Minerva Anestesiol* 2006; 72: 69-80.
15. Castelli GP, Pognani C, Cita M, Paladini R. Procalcitonin as a prognostic and diagnostic tool for septic complications after major trauma. *Crit Care Med* 2009 (in press).
16. Rey C, Los AM, Concha A, Medina A, Prieto S, Martinez P et al. Procalcitonin and C-reactive protein as markers of systemic inflammatory response syndrome severity in critically ill children. *Intensive Care Med* 2007; 33: 477-484.
17. Jensen JU, Heslet L, Jensen TH, Espersen K, Steffensen P, Tvede M. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. *Crit Care Med* 2006; 34: 2596-2602.
18. Lee CC, Chen SY, Tsai CL, Wu SC, Chiang WC, Wang JL, Sum HY, Chen SC, Chen WJ, Hsueh PR. Prognostic Value of MEDS Score, Procalcitonin and CRP in Patients with Sepsis at the Emergency Department. *Shock* 2008; 29: 322-327.
19. Reinhart K, Brunkhorst F, Bone H, Gerlach H, Gründling M, Kreyman G, Kujath P, Marggraf G, Mayer K, Meier-Hellmann A, Peckelsen C, Putensen C, Quintel M, Ragaller M, Rossaint R, Stüber F, Weiler N, Welte T, Werdan K. Diagnosis and therapy of sepsis. Guidelines of the German Sepsis Society Inc. and the German Interdisciplinary Society for Intensive and Emergency Medicine. *Internist* 2006; 47: 356-373.

ABBREVIATIONS

ARDS	Acute respiratory distress syndrome
BT	Body temperature
CAP	Community-acquired pneumonia
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CSF	Cerebro-spinal fluid
CT	Calcitonin
CT-scan	Computed tomography scan
CURB65	Confusion, serum Urea, Respiratory rate, Blood pressure and age ≥ 65 (scoring system for severity of pneumonia)
CXR	Chest X-ray
DNA	Deoxynucleic acid
ED	Emergency department
GCS	Glasgow coma scale
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICU	Intensive care unit
ID	Infectious diseases
IL	Interleukin
LRTI	Lower respiratory tract infection
MEDS	Mortality in Emergency Department Sepsis (risk stratification score)
mRNA	Messenger riboxynucleic acid
NI	Non-infectious
NPV	Negative predictive value
PCT	Procalcitonin
PSI	Pneumonia severity index
RBC	Red blood count
SAPS	Simplified acute physiology score
SIRS	Severe inflammatory response syndrome
TISS	Therapeutic intervention scoring system
TNF	Tumor necrosis factor
VAP	Ventilator-associated pneumonia
WBC	White blood count



PCT