thermoscientific

Informing Antibiotic Decisions in Patients with LRTI

B·R·A·H·M·S PCT
A valuable tool for aiding antibiotic stewardship

B·R·A·H·M·S PCT™ PROVEN CONFIDENCE

ThermoFisher SCIENTIFIC

Understanding Procalcitonin (PCT)

The utility of B·R·A·H·M·S PCT™ as a tool for informing antibiotic therapy decisions stems from its unique kinetics in response to systemic bacterial infection.

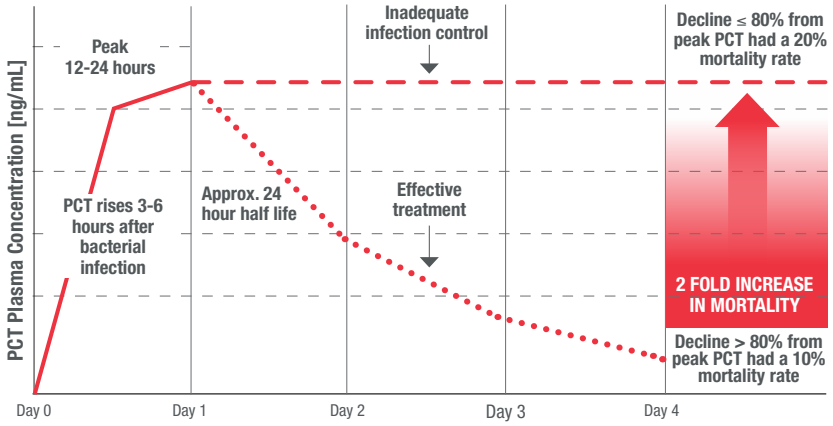
PCT is an immunoactive molecule involved in the body's immune response to bacterial infection. PCT can be produced by several cell types and organs in response to pro-inflammatory stimuli by bacteria.[1] In healthy individuals, PCT concentrations are less than 0.1 ng/mL.[2] PCT levels increase 2 to 3 hours after bacterial insult and peak within 12 to 24 hours.[3,4,5] The magnitude of the increase in PCT concentration correlates with the severity of the bacterial infection.[4]

As the bacterial infection is controlled with appropriate antibiotic therapy, PCT levels decrease by up to 50% per day.[6,7] If therapy is inadequate, bacteria will continue to stimulate PCT production and levels will remain high.

During viral infections, PCT production is attenuated by interferon-γ released during the host response to the virus, and thus will not rise as in bacterial infections.

PCT Kinetics Highlights

- **Levels increase 2-3 hours after bacterial insult and return to normal as the infection is resolved.[3,4,5]**
- **Approximate half-life of 24 hours**
- **High specificity and sensitivity for bacterial infection**
- **Indicator for disease severity and treatment response**



Comparing PCT to Other Biomarkers

Lactate

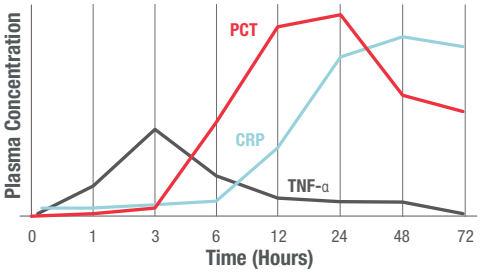
A marker of inadequate tissue perfusion, lactate (lactic acid) is not specific for bacterial infection; a wide range of clinical conditions can increase lactate levels.[5] Lactate does not rise until late in the course of systemic bacterial infection.[8] For patients evaluated in the ED for a suspected infection, the combination of lactate and PCT measurements, together with clinical data and vital signs, provide complementary information for risk stratification.[9]

C-Reactive Protein (CRP)

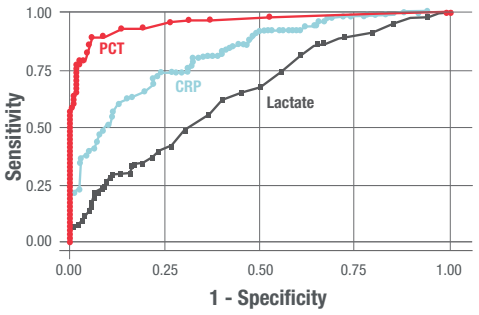
CRP is triggered in response to inflammation associated with bacterial, viral, or fungal infection, and conditions such as obesity and tissue injury. It has no correlation to Sepsis-related Organ Failure Assessment (SOFA) score and its kinetics are slow, peaking 36 to 50 hours after causal challenge.[10,11,12] CRP has not been recommended because of its lack of specificity for systemic bacterial infection and its suppression when corticosteroids are used.[13]

Blood Cultures

Only 30% – 50% of patients with a clinical diagnosis of severe sepsis or septic shock have positive blood cultures.[14] Challenges with relying on blood cultures for assessing systemic infection include the delay for response, decreased sensitivity in patients already on antibiotics, and potential for false-positive results due to sample contamination.



The unique kinetics of PCT make it a valuable complement to other biomarkers of systemic infection and sepsis.[15]



PCT has the best AUC as a marker of systemic bacterial infection, compared to CRP and Lactate.[16]

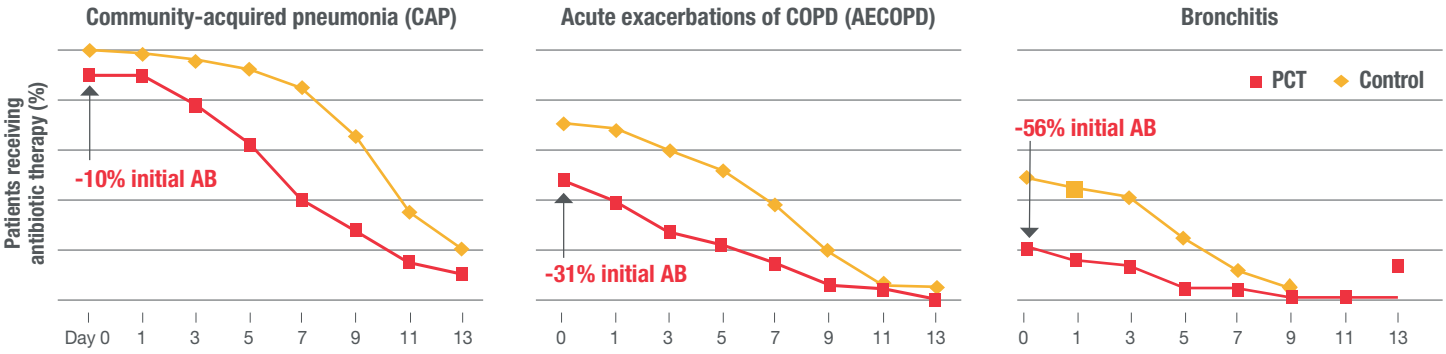
LRTI: Is it Bacterial or Viral?

As many as 75% of patients with acute respiratory-tract infections are treated with antibiotics, despite a mainly viral cause for these infections.[17]

B·R·A·H·M·S PCT has been shown to aid clinicians in the emergency room or inpatient hospital settings in determining whether antibiotics are appropriate for patients with suspected or confirmed lower respiratory tract infections (LRTI), defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD).[18, 19-27]

B·R·A·H·M·S PCT has been shown to reduce antibiotic prescription rate and exposure duration in LRTI.

Duration of antibiotic exposure and antibiotic prescription rates were significantly reduced in the PCT group in comparison to the standard of care group for community-acquired pneumonia (CAP) (n=925), acute exacerbations of COPD (n=228) and bronchitis (n=151) in the ProHOSP trial.[18]



Fewer antibiotics were initiated in the PCT-guided group.

Guiding Antibiotic Therapy Decisions for LRTI

PCT Thresholds

PCT Plasma Concentration [ng/mL]

> 0.50 ng/mL	Antibiotics Strongly Encouraged
> 0.25 – 0.50 ng/mL	Antibiotics Encouraged
0.10 – 0.25 ng/mL	Antibiotics Discouraged
< 0.10 ng/mL	Antibiotics Strongly Discouraged

Insight for Safely Discontinuing Antibiotic Therapy

Paired with clinical assessment, B·R·A·H·M·S PCT also aids decisions about whether to discontinue antibiotic therapy for patients with LRTI.

Change in PCT Plasma Concentration

Decline from peak PCT > 80% *and* Clinical Improvement

OR

Current PCT Plasma Concentration

Sepsis	≤ 0.50 ng/mL Discontinue Antibiotics
LRTI	≤ 0.25 ng/mL Discontinue Antibiotics

PCT-guided therapy has been shown to aid antibiotic stewardship for LRTI:[18,21,22,24-34]

19.2% reduction in relative antibiotic initiation

38% reduction in antibiotic exposure (3.6 days) for inpatients

51% reduction in antibiotic exposure for ED patients not admitted

No negative effects for mortality or length of stay

Clinical Challenge: Is it Heart Failure or LRTI?

In patients with a history of congestive heart failure (CHF) presenting with acute respiratory symptoms, differentiating acute heart failure (AHF) from LRTI is challenging due to overlapping clinical presentation and radiological findings.[35]

- **18% of hospitalizations for acute heart failure are caused by infections.[36]**
- **Infection (e.g. pneumonia, infective endocarditis, sepsis) is a known factor in triggering AHF.[31]**
- **Pneumonia is independently associated with higher in-hospital mortality for hospitalized heart failure patients (Odds Ratio 1.60).[38]**
- **AHF precipitated by ACS or infection is independently associated with higher 90-day risk of death (Hazard Ratio 1.51).[39]**

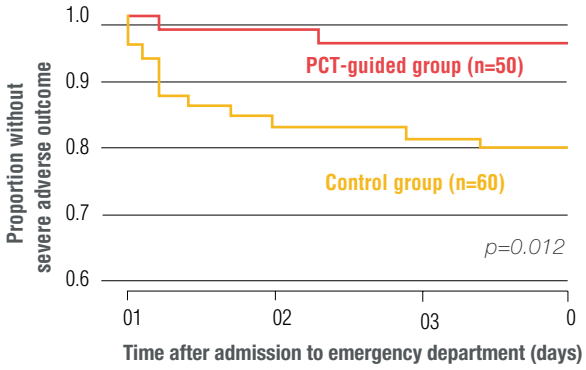
PCT-guided Antibiotic Therapy in HF Patients with Suspected Pneumonia

Secondary analysis of 233 patients with a history of CHF, formerly included in a multicenter, randomized-controlled trial, to compare antibiotic guidance with and without PCT algorithm.[40]

In 110 patients with low initial PCT value (<0.25 ng/mL):

- **30-day adverse outcome was significantly decreased (-16%) in PCT-guided group.**
- **Antibiotic exposure was significantly reduced (-2.8 days) in PCT-guided group.**

For patients presenting with dyspnea, PCT >0.25ng/mL indicates bacterial infection that requires antibiotic treatment.[40]



Time to the first adverse outcome by randomization group in patients with low initial PCT levels (<0.25 ng/mL); adverse outcome included all-cause mortality or ICU admission.[40]

B·R·A·H·M·S PCT results should be evaluated in context of all laboratory findings and the total clinical status of the patient. Decisions regarding antibiotic therapy should not be based solely on procalcitonin concentrations.

B·R·A·H·M·S PCT: The Quality Standard

When using PCT assays to support clinical decisions, quality and experience count. Clinicians worldwide rely on B·R·A·H·M·S PCT quality to make confident patient care decisions due to:

- **Evidence:** 4000+ publications in both the U.S. and Europe demonstrate the clinical utility of PCT.
- **Experience:** B·R·A·H·M·S PCT has been in clinical use since 1996.
- **Standardization:** Standardized clinical cut-offs, independent of platform.
- **Precision:** Demonstrated high clinical equivalence to the B·R·A·H·M·S PCT reference.
- **Adoption:** PCT is included in antibiotic stewardship guidelines issued by IDSA (Infectious Disease Society of America) and the Surviving Sepsis Campaign.[41,42]

ThermoFisher SCIENTIFIC

References

1. Christ-Crain, et al., Swiss Med Wkly 2005; 135: 451-460. Procalcitonin in bacterial infections: Hype, Hope, more or less?
2. Morgenthaler N.G., Struck J. et al., Clin Lab 2002: 48(5-6): 263-270. Detection of procalcitonin (PCT) in healthy controls and patients with local infection by a sensitive ILMA.
3. Harbarth et al., Am J Respir Crit Care Med 2001; 164: 396-402
4. Meisner M, Procalcitonin – Biochemistry and Clinical Diagnosis, ISBN 978-3-8374-1241-3, UNI-MED, Bremen 2010.
5. Müller B et al., Crit Care Med 2000, 28 (4): 977-983.
6. Luyt C.E. et al., Am. J. Resp. Crit. Care Med 2005; 171(1) 48-53. Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia.
7. Brunkhorst F.M. et al., Intensive Care Med. 1998; 24: 888-892. Kinetics of procalcitonin in iatrogenic sepsis.
8. Thomas-Rueddel DO et al: Hyperlactatemia is an independent predictor of mortality and denotes distinct subtypes of severe sepsis and septic shock. J Crit Care 2015;30(2):439. e1-439.e6.
9. Freund Y: Serum lactate and procalcitonin measurements in emergency room for the diagnosis and risk-stratification of patients with suspected infection. Biomarkers 2012;17(7):590-596.
10. Blomkalns AL: Sick or Not Sick? Evolving biomarkers for severe bacterial infection. 2007;7(November). Emergency Medicine Cardiac Research and Education Group.
11. Vigushin DM: Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. J Clin Invest 1993;91(4):1351-1357.
12. Pepys MB et al: C-reactive protein: a critical update. J Clin Invest 2003;111(12):1805-1812.
13. Standage SW et al: Biomarkers for pediatric sepsis and septic shock. Expert Rev Anti Infect Ther 2011;9(1):71-79.
14. Morgenthaler NG et al: Detection of procalcitonin (PCT) in healthy controls and patients with local infection by a sensitive ILMA. Clin Lab 2002;48(5-6):263-270.
15. Meisner M. Procalcitonin: Experience with a new diagnostic tool for bacterial infection and systemic inflammation. J Lab Med 1999;23:263-72.
16. Müller B et al: Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. Critical Care Medicine 2000;28(4):977-983.
17. Macfarlane J, Lewis SA, Macfarlane R, Holmes W. Contemporary use of antibiotics in 1089 adults presenting with acute lower respiratory tract illness in general practice in the U.K. Respir Med. 1997;91(7): 427-434.
18. Schuetz P., Christ-Crain M. et al., Jama 2009; 302(10): 1059-1066. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial.
19. Burkhardt O. et al., Eur. Resp. J. 2010; 36(3): 601-7. Procalcitonin guidance and reduction of antibiotic use in acute respiratory tract infection.
20. Christ-Crain M. et al., Am. J. Resp. Crit. Care Med. 2006; 174: 84–93. Procalcitonin Guidance of Antibiotic Therapy in Community-acquired Pneumonia.
21. Hochreiter M. et al., Crit Care 2009; 13(3), R83. Procalcitonin to guide duration of antibiotic therapy in surgical intensive care patients: a randomized prospective controlled trial.
22. Kristoffersen K. B. et al., Clin. Microbiol. Infect. 2009; 15(5): 481-7. Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission–a randomized trial.
23. Long W. et al., Respirology. 2011; 16(5): 819-24. Procalcitonin guidance for reduction of antibiotic use in low-risk outpatients with community-acquired pneumonia.
24. Nobre V. et al., Am. J. Resp. Crit. Care Med. 2008; 177: 498–505. Use of Procalcitonin to Shorten Antibiotic Treatment Duration in Septic Patients: A Randomized Trial.
25. Schroeder S. et al., Langenbecks Arch Surg 2009;394(2): 221-6. Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomized study.
26. Stolz D.et al., Chest 2007; 131(1): 9-19. Antibiotic Treatment of Exacerbations of COPD: A Randomized, Controlled Trial Comparing Procalcitonin-Guidance With Standard Therapy.
27. Stolz D. et al.; Eur. Respir. J. 2009; 34(6): 1364-75. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study.
28. Bouadma L., Luyt C. E. et al., Lancet 2010; 375(9713): 463-474. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial.
29. Briel M. et al., Arch Intern Med. 2008; 168(18): 2000-7. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care.
30. Burkhardt O. et al., Eur. Resp. J. 2010; 36(3): 601-7. Procalcitonin guidance and reduction of antibiotic use in acute respiratory tract infection.
31. Christ-Crain M. et al., Lancet 2004; 363(9409):600-7. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial.
32. Christ-Crain M. et al., Am. J. Resp. Crit. Care Med. 2006; 174: 84–93. Procalcitonin Guidance of Antibiotic Therapy in Community-acquired Pneumonia.
33. Long W. et al., Respirology. 2011; 16(5): 819-24. Procalcitonin guidance for reduction of antibiotic use in low-risk outpatients with community-acquired pneumonia.
34. Long W. et al., Zhonghua Nei Ke Za Zhi 2009; 48(3):216-9. The value of serum procalcitonin in treatment of community acquired pneumonia in outpatient.
35. Tsuyuki et al., Arch Intern Med 2001; 161(19): 2337-42. Acute precipitants of congestive heart failure exacerbations.
36. Nieminen et al., Eur Heart J 2006; 27(22): 2725-36. EuroHear Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population.
37. Ponikowski et al., Eur Heart J 2016; 37(27), 2129–2200. 2016 Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC.
38. Fonarow et al., Arch Intern Med 2008; 168(8): 847-54. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF.
39. Arrigo et al., Eur J Heart Fail 2017 Feb; 19(2): 201-208. Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry.
40. Schuetz et al., Int J Cardiol 2014; 175(3): 464-72. Excluding infection through procalcitonin testing improves outcomes of congestive heart failure patients presenting with acute respiratory symptoms: results from the randomized ProHOSP trial.
41. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2016.
42. Barlam T, et al., Guideline for Implementing an Antibiotic Stewardship Program, Infectious Diseases Society of America, CID 2016:62.

Clinical Diagnostics

Germany:

Thermo Fisher Scientific
B·R·A·H·M·S GmbH
Neuendorfstr. 25
16761 Hennigsdorf,
Germany

+49 (0)3302 883 0
+49 (0)3302 883 100 fax
info.brahms@thermofisher.com
www.thermofisher.com/brahms

USA:

Thermo Fisher Scientific
8365 Valley Pike
Middletown, VA 22645

(800) 232 3342
customerservice.diagnostics.mtn@thermofisher.com
www.thermofisher.com/aboutsepsis

Find out more at **thermofisher.com/aboutsepsis**

ThermoFisher SCIENTIFIC

900883.1