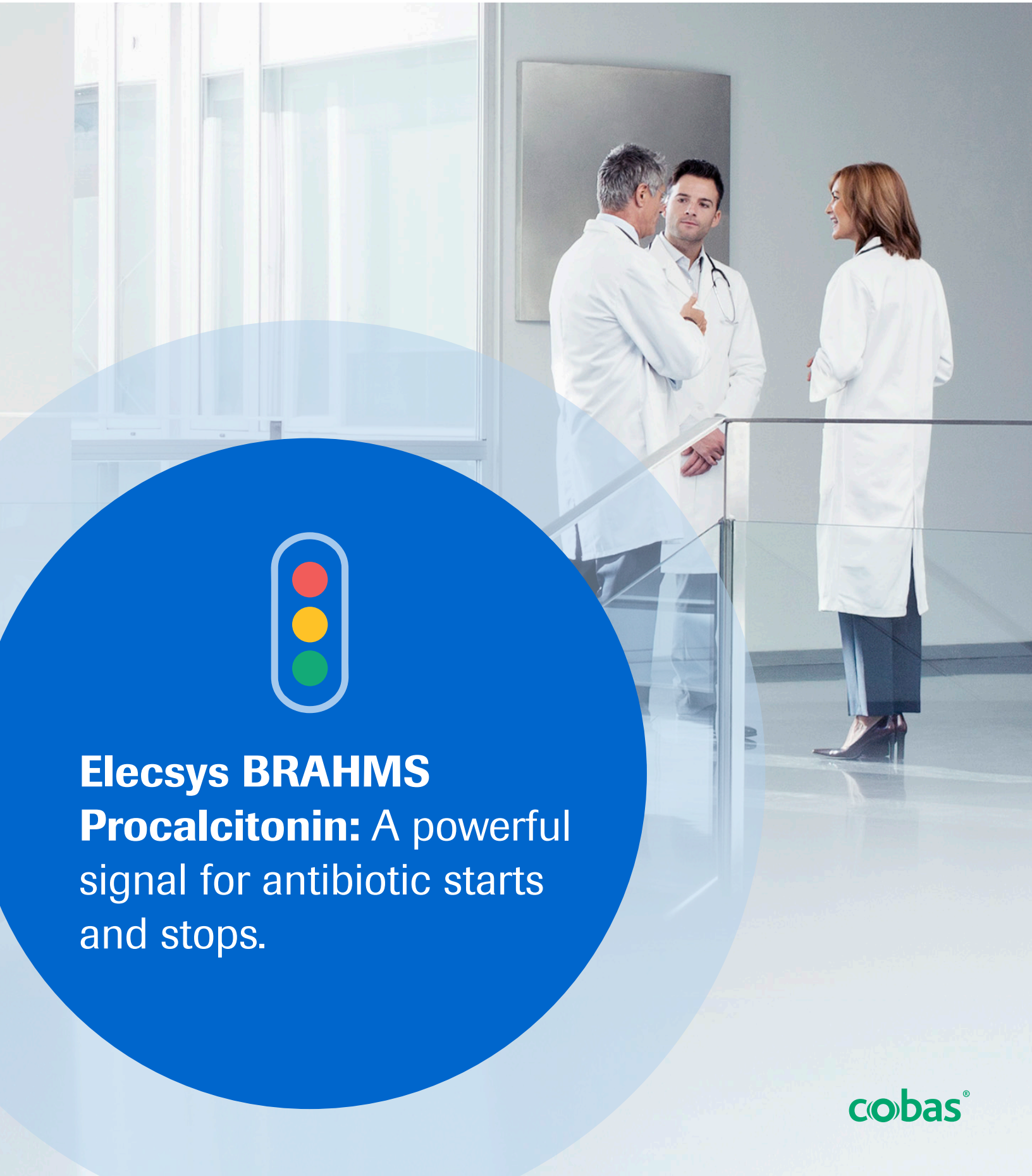


Elecsys BRAHMS Procalcitonin: A powerful signal for antibiotic starts and stops.

About PCT

Procalcitonin (PCT) provides clinicians a sensitive and specific biomarker associated with the inflammatory response to bacterial infection to aid sepsis mortality risk assessment and as a tool in antibiotic stewardship programs.[1] In conjunction with other laboratory findings and clinical assessments, PCT provides valuable information on the severity of a bacterial infection — both on presentation and during the course of treatment.[2]

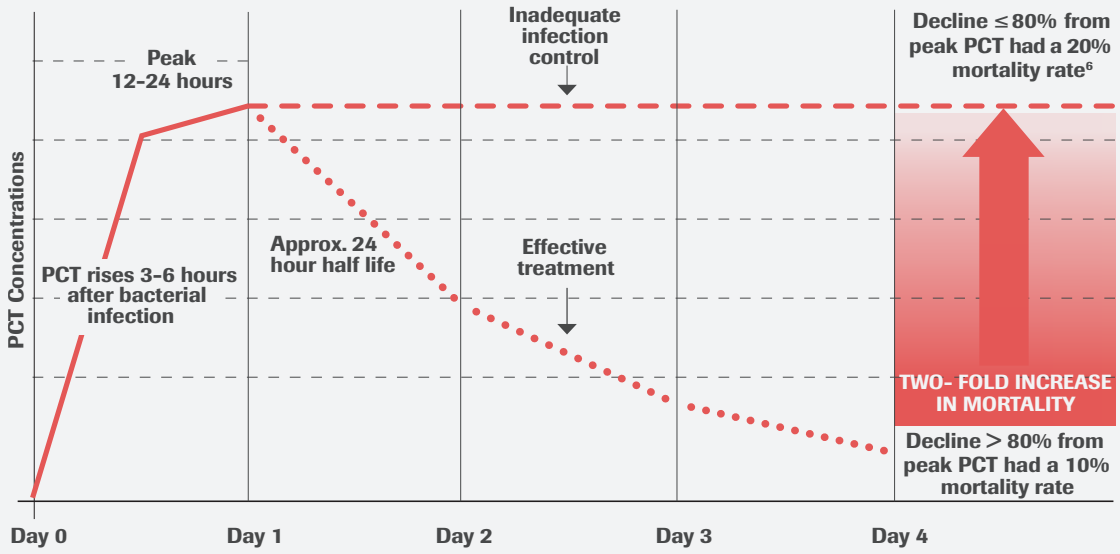
In healthy individuals, PCT concentrations are found to be below 0.1 ng/mL.[3] Depending on the clinical background, a PCT concentration above 0.1 ng/mL can indicate a clinically relevant bacterial infection, requiring antibiotic treatment.[4] PCT levels rise rapidly (within 3-6 hours) after a bacterial insult with systemic consequences. The magnitude of the increase in PCT concentration correlates with the severity of the bacterial infection. This correlation provides clear signals to support antibiotic decision making for patients with suspected or confirmed sepsis, pneumonia and other conditions caused by bacterial infections.

PCT Kinetics[5]

PCT concentrations increase 3-6 hours after bacterial insult and return to normal as the infection is resolved.

- Approximate half-life of 24 hours
- High specificity and sensitivity for bacterial infection
- Indicator of infection severity and antibiotic treatment response

PCT values rise in relation to bacterial infection[5]



Understanding PCT Kinetics

When a bacterial infection occurs, toll-like receptors flag the presence of microbial toxins. Inflammatory cytokines, such as Interleukin 1 beta (IL-1ß), Tumor Necrosis Factor alpha (TNF-α), and Interleukin 6 (IL-6) are simultaneously secreted from the cell. Signaling pathways then stimulate PCT transcription, typically over 3 to 6 hours.[7,8]

If the pathogen is not contained, infection spreads and the body up-regulates pro-inflammatory mediators, causing a dramatic increase in serum PCT for another 12 to 24 hours.[9]

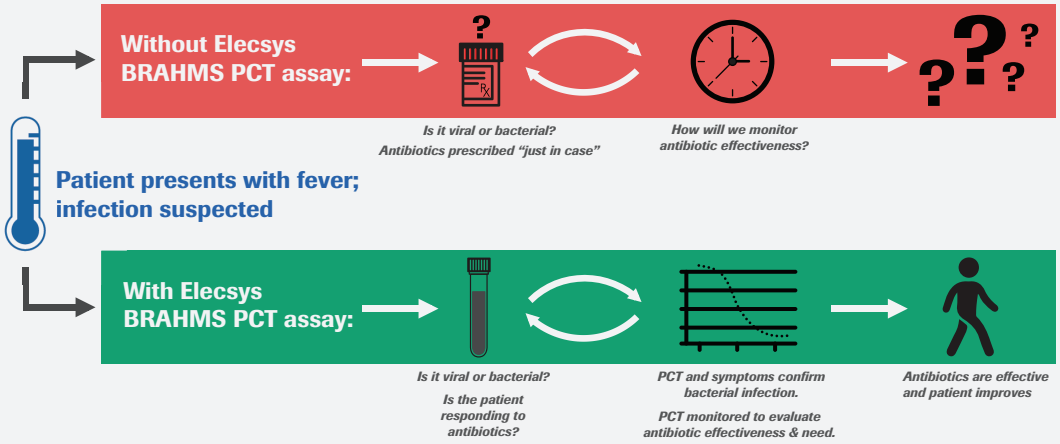
It can take nearly 24 hours of appropriate antibiotic therapy to see reduction in serum PCT levels as the bacterial infection is controlled, which will be reflected in a decrease in PCT production and serum concentrations by up to 50% per day. **However, if initial antibiotic therapy or source control is not adequate, bacteria will continue to stimulate PCT production and blood concentrations will remain high.[10]**

During viral infections, PCT production is lessened by Interferon gamma (IFN-γ) that is released during the host response to the virus.[10] **Thus, PCT concentration will not rise in viral infections as it does in the presence of a bacterial infection.**

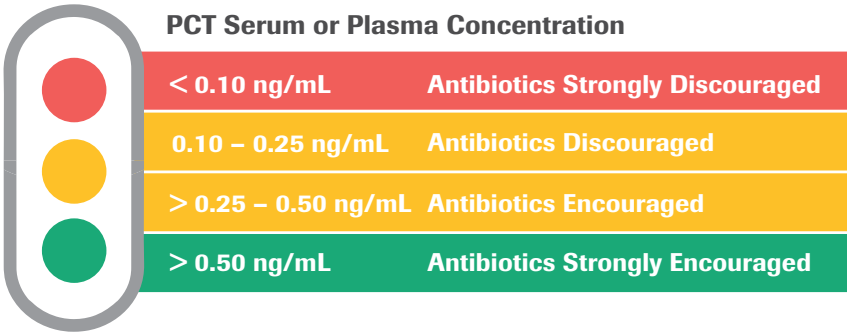
The utility of PCT as a tool for assessing the risk of bacterial infection stems from its unique kinetics, triggered from the inflammatory response to a bacterial infection.

A clear signal for LRTI antibiotic decisions[1]

As many as 71% of patients with acute respiratory-tract infections are treated with antibiotics, despite a mainly viral cause for these infections.[12] Elecsys BRAHMS PCT aids clinicians 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).



PCT cut-offs in LRTI patients[1]

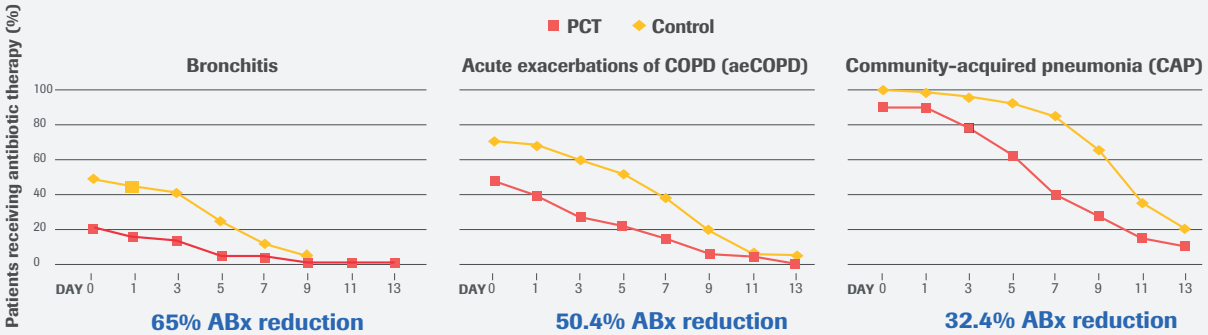


PCT-guided therapy has been shown to reduce inpatient antibiotic exposure by 35% for LRTI patients[11,] and 23%[13] for critically ill ICU patients[12-23] without negative effects on mortality or length of stay.

BRAHMS PCT has been shown to reduce antibiotic prescription rate and exposure duration in LRTI[12]

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.[12]

PCT-supported decision making reduces unnecessary ABx exposure



A clear signal when managing critically ill sepsis patients

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[24]

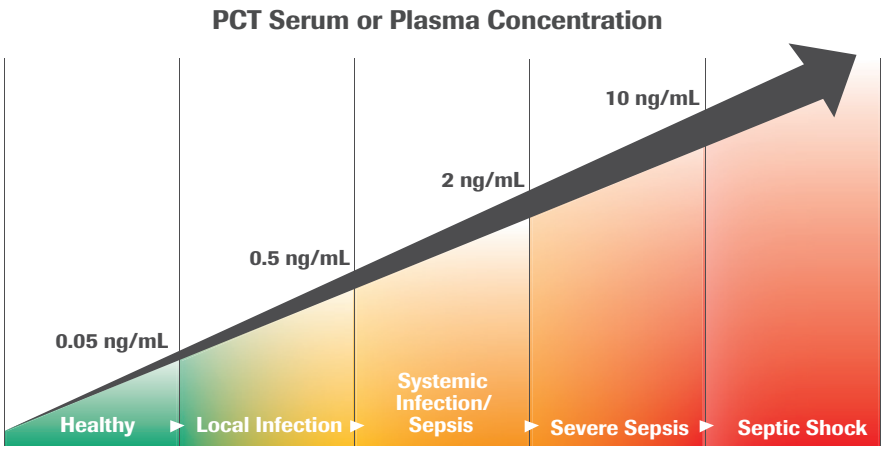
Sepsis is a public health crisis that impacts more than 1.5 million Americans each year - or one person every 20 seconds.[25] According to the Centers for Disease Control and Prevention, > 250,000 people die from sepsis each year - more than AIDS, stroke, and prostate and breast cancer combined.

> 50% of patients who die in hospitals have sepsis[26] and managing these patients makes sepsis the most costly inpatient diagnosis, with aggregate annual hospital costs totaling $24 billion.[27]

While as many as 80% of sepsis deaths could be prevented with rapid diagnosis and treatment,[28] achieving this can be challenging due to the non-specific signs and symptoms associated with sepsis.

Aiding Assessment of Mortality Risk

As a sensitive and specific biomarker of the inflammatory response to bacterial infection, Elecsys BRAHMS PCT aids clinicians in determining a critically ill patient's risk of progression to sepsis and septic shock.

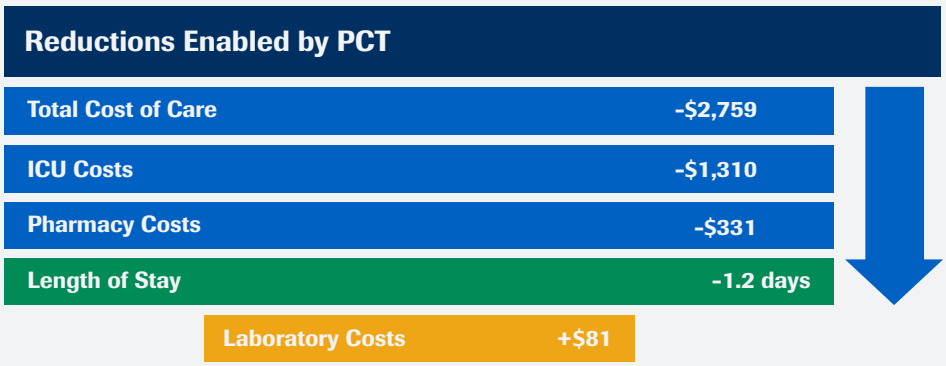


5,18,23

Following ICU admission and the diagnosis of sepsis, evaluating serial Elecsys BRAHMS PCT measurements over consecutive days aids in assessing the host response to antibiotic therapy and the risk of all-cause mortality. When the infection is controlled, PCT will decline daily.[29] If the PCT level has not declined, the patient and therapy should be reassessed.

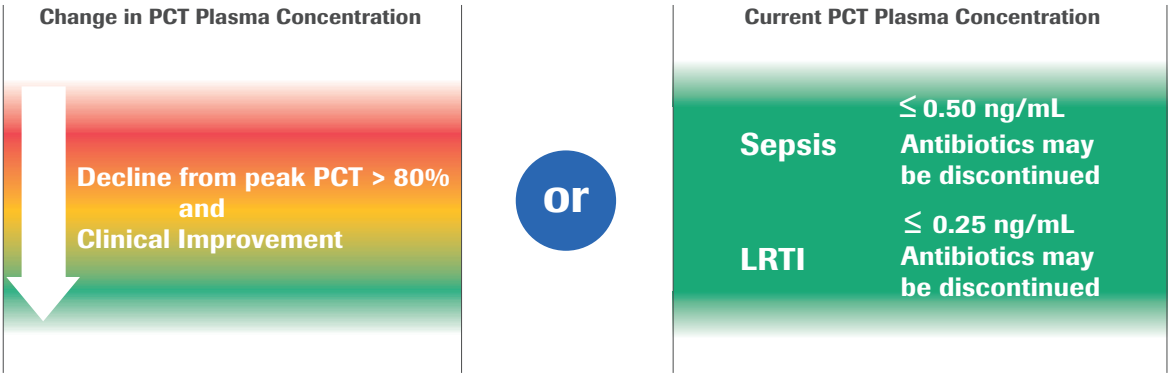
PCT testing in the ICU is associated with significantly lower costs and lengths of stay

A recent analysis of > 619 million patient encounters in the Premier Healthcare Database over 3 1/2 years found that the use of PCT testing on the first day of ICU admission was associated with significant resource savings and length of stay reductions.[30]



Insight for Safely Discontinuing Antibiotics[1]

Paired with clinical assessment, Elecsys BRAHMS PCT also aids decisions whether to discontinue antibiotic therapy for patients with suspected or confirmed sepsis.



About the U.S. Multicenter MOSES Study[31]

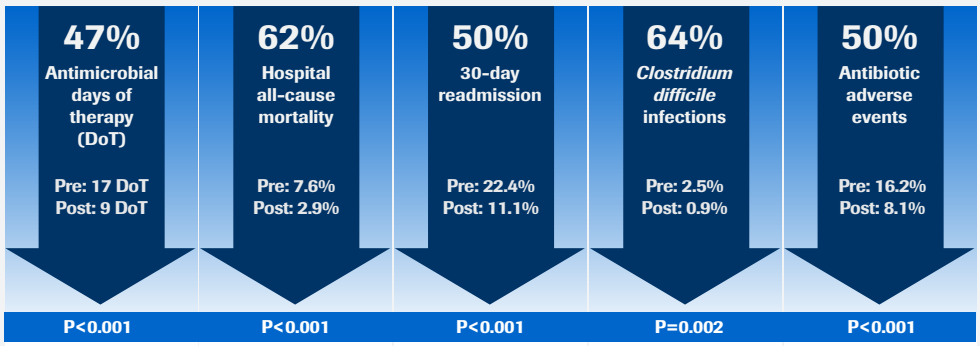
The Procalcitonin Monitoring Sepsis Study (MOSES) included 858 adult patients with sepsis recruited across 13 investigational sites in the U.S.

Key findings of the study included:

- The change of PCT over time aids in assessing the cumulative 28-day risk for all-cause mortality for patients diagnosed with severe sepsis or septic shock.
- A two-fold increased risk of death is seen for patients showing a decrease in PCT≤ 80% during the first four days following diagnosis of severe sepsis or septic shock compared to those who experienced a decrease in PCT > 80%. Mortality was the same for both men and women.
- The initial PCT level (≤ 2.0 ng/mL or > 2.0 ng/mL) provided important additional information about the mortality risk when evaluating the patient's clinical course with PCT measurements on subsequent days.

PCT can help reduce antibiotic use by providing diagnostic clarity on bacterial infection management

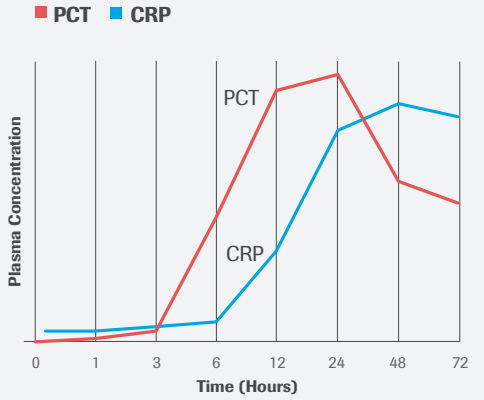
Procalcitonin integrated into antibiotic stewardship programs can result in significant reductions in antibiotic days on therapy (DOT) and certain adverse outcome measures, as shown by Michael Broyles, PharmD, in a 2017 study at Five Rivers Medical Center: Impact of Procalcitonin (PCT)-Guided Antibiotic Management on Antibiotic Exposure and Outcomes: Real World Evidence.[32]



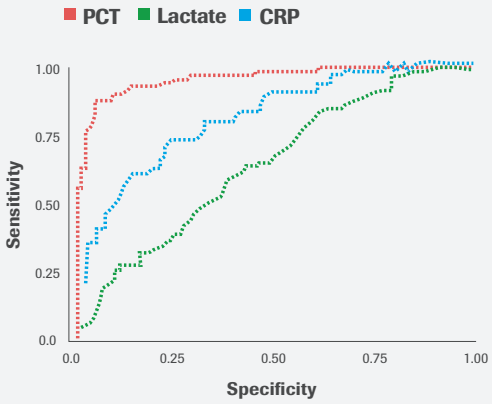
Comparing PCT to Other Biomarkers

The sensitivity and specificity of PCT in the host response to systemic bacterial infection, together with its rapid rise after an infectious challenge, offer clinical advantages that complement existing biomarkers in the clinical assessment of the septic patient.[2]

The unique kinetics of PCT make it a valuable complement to CRP.[33]



PCT's sensitivity and specificity as a marker of systemic bacterial infection make it a valuable complement to traditional biomarkers used in sepsis risk assessment.[34]



Lactate

Lactate (lactic acid) is produced due to inadequate tissue perfusion, a defining parameter of late sepsis. Reduction of lactate is advocated as a target for therapeutic interventions.[32] However, lactate is NOT specific for bacterial infection nor do levels of lactate correlate with the host response to bacterial infection.

C-Reactive Protein (CRP)

CRP secretion is triggered by cytokines (IL-6, IL-1ß, TNF-α) in response to acute or chronic 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.[33-35] In recent years, CRP has not been recommended because of its lack of specificity for systemic bacterial infection and its suppression when corticosteroids are used.[2]

Blood cultures

Despite recent advances, blood cultures often lack the sensitivity to identify the infecting pathogen in severe sepsis and septic shock. Only 30-40% of patients with a clinical diagnosis of severe sepsis or septic shock have positive blood cultures[39] and the delay in results due to slow-growing organisms and decreased sensitivity in patients already receiving antibiotics can introduce additional challenges.

Roche Diagnostics: A Leader in Raising Sepsis Awareness

Roche Diagnostics is committed to leading the fight against sepsis.

With its partner, the Rory Staunton Foundation, resources are committed to advance the understanding of sepsis and encourage awareness, assessment and prevention.

Why? Simply, to ensure that the 80% of sepsis deaths that can be prevented with rapid diagnosis and optimal treatment are prevented.[28]

THE RORY STAUNTON FOUNDATION
FOR SEPSIS PREVENTION

BRAHMS PCT: The Quality Standard

When using PCT assays to support clinical decisions, quality and experience counts. Clinicians worldwide have relied on BRAHMS PCT since 1996 to make patient care decisions with confidence due to:

Evidence: 3,500+ publications in both the U.S. and Europe demonstrate the clinical utility of PCT.

Precision: Highly precise at clinically relevant cut-offs.

Adoption: PCT is included in antibiotic stewardship guidelines issued by the Infectious Disease Society of America (IDSA) and the Surviving Sepsis Campaign Guidelines issued by the Society of Critical Care Medicine (SCCM).[4,5]

Elecsys® BRAHMS PCT Indications

Indications for Use[1]

Used in conjunction with other laboratory findings and clinical assessments, the Elecsys BRAHMS PCT assay is intended for use as an:

- Aid in risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock.
- Aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission, using a change in PCT level over time.

Antibiotic initiation and deescalation claims:

- Aid in decision making on antibiotic therapy for patients with suspected or confirmed lower respiratory tract infections (LRTI)—defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbations of chronic obstructive pulmonary disease (aeCOPD)—in an inpatient setting or an emergency department.
- Aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

When using Elecsys BRAHMS PCT for ICU patient management, comparing the baseline PCT level taken on Day 0/1 with subsequent measurements through Day 4, the following assessments of PCT kinetics should be considered:

- Decrease in PCT values greater than 80% = lower risk of all-cause 28-day mortality
- Decrease in PCT values less than or equal to 80% = higher risk of 28-day all-cause mortality
- Baseline PCT measurement less than or equal to 2.0 ng/mL or greater than 2.0 ng/mL = provides additional information about the mortality risk when evaluating the patient's clinical course with PCT measurements on subsequent days.

PCT level should always be used in conjunction with other clinical assessments and laboratory findings, not in isolation.

Important Considerations When Interpreting PCT Results

Increased PCT levels may not always be related to systemic bacterial infection.[2, 37-39]
They may also be associated with:

- Injuries including major trauma, burns and heat stroke
- Acute medical conditions, such as biliary pancreatitis, chemical pneumonitis, viral hepatitis and/or decompensated severe cirrhosis (Child-Pugh Class 3), prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, and post-cardiac arrest
- Unusual infectious diseases, including invasive fungal infections and acute plasmodium falciparum malaria
- Active medullary C-cell carcinoma, small cell lung carcinoma and bronchial carcinoid
- Interventions such as surgery with extracorporeal circulation, treatment with drugs stimulating release of pro-inflammatory cytokines or resulting in anaphylaxis, peritoneal or hemodialysis
- Neonates during the first two days of life

Elecsys® BRAHMS PCT results should be evaluated in context of all laboratory findings and the total clinical status of the patient. In cases where the laboratory results do not agree with the clinical picture or history, additional tests should be performed. Refer to Roche Diagnostics Elecsys® BRAHMS PCT package insert for additional information.

References

1. Elecsys BRAHMS Procalcitonin Package Insert 2018.
2. Meisner M. Procalcitonin – Biochemistry and Clinical Diagnosis. 1st ed. Germany: UNI-MED Science; 2010
3. Morganthaler NG, Struck J, Fischer-Schultz C, 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.
4. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet. 2004;363(9409):600-607.
5. Elecsys BRAHMS PCT package insert.
6. MOSES study - Procalcitonin Monitoring Sepsis Study; ClinicalTrials.gov Identifier: NCT01523717.
7. Müller B, White JC, Nylén ES, Snider RH, Becker KL, Habener JF. Ubiquitous expression of the calcitonin-I gene in multiple tissues in response to sepsis. J Clin Endocrinol Metab. 2001;86(1):396-404.
8. Becker KL, Nylén ES, White JC, Müller B, Snider RH Jr. Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. J Clin Endocrinol Metab. 2004;89(4):1512-1525.
9. Meisner M. Procalcitonin (PCT): A New, Innovative Infection Parameter. Biochemical and Clinical Aspects. Stuttgart, Germany: Thieme Medical Publishers; 2000.
10. Samraj, Ravi S., Basilia Zingarelli, and Hector R. Wong. "Role of Biomarkers in Sepsis Care." Shock (Augusta, Ga.) 40.5 (2013): 358–365. PMC. Web. 6 Feb. 2018.
11. Schuetz P, Christ-Crain M et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. Jama. 2009;302(10):1059-1066.
12. 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
13. 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.
14. 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.
15. Burkhardt O. et al., Eur. Resp. J. 2010; 36(3): 601-7. Procalcitonin guidance and reduction of antibiotic use in acute respiratory tract infection.
16. Christ-Crain M. et al., Am. J. Resp. Crit. Care Med. 2006; 174: 84–93. Procalcitonin Guidance of Antibiotic Therapy in Community-acquired Pneumonia.
17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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.
23. Stolz D. et al.; Eur. Respir. J. 2009; 34(6): 1364-75. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study.
24. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–810. doi:10.1001/jama.2016.0287
25. Centers for Disease Control. Available at: https://www.cdc.gov/sepsis/datareports/index.html. Accessed November 8, 2017.
26. Vincent L, Escobar GJ, Greene JD, et al. Hospital Deaths in Patients With Sepsis From 2 Independent Cohorts. Available at: https://jamanetwork.com/journals/jama/fullarticle/1873131. Accessed November 8, 2017.
27. Sepsis Alliance. Sepsis fact sheet. http://www.sepsis.org/downloads/2016_sepsis_facts_media.pdf. Accessed July 20, 2016.
28. Kumar A, et al.; Crit Care Med. 2006 Jun;34(6):1589-96. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock
29. Soni NJ, Samson DJ, Galaydick JL, et al. Procalcitonin-guided antibiotic therapy: a systematic review and meta-analysis. J Hosp Med. 2013;8(9):530-540.
30. Balk A, et al. Effect of Procalcitonin Testing on Health-care Utilization and Costs in Critically Ill Patients in the United States. Chest. 2017 Jan; 151(1):23-33. Available at: https:doi.org/10.1016/j.chest.2016.06.046. Accessed November 8, 2017.
31. Moses Clinical Trial. Data on file. Thermo Fisher Scientific.
32. Broyles, PharmD, Michael R., Impact of Procalcitonin-Guided Antibiotic Management on Antibiotic Exposure and Outcomes: Real-world Evidence, Open Forum Infectious Diseases, Volume 4, Issue 4, 1 October 2017, ofx213, https://doi.org/10.1093/ofid/ofx213
33. Meisner M. Procalcitonin: Experience with a new diagnostic tool for bacterial infection and systemic inflammation. J Lab Med 1999;23:263-72.
34. 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.
35. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41 (2): 580-637.
36. Vigushin DM, Pepys MB, Hawkins PN. Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. J Clin Invest. 1993;91(4):1351-1357.
37. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003:111(123:1805-1812.
38. Standage SW, Wong HR. Biomarkers for pediatric sepsis and septic shock. Expert RevAnti Infect Ther. 2011 ;9(1):71 -79.
39. ProCESS Investigators; Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370(18):1683-1693.
40. Meisner M, Tschaikowsky K, Hutzler A, Schick C, Schüttler J. Postoperative plasma concentrations of procalcitonin after different types of surgery. Intensive Care Med.1998;24(7): 680-684.
41. Chiesa C, Panero A, Rossi N, et al. Reliability of procalcitonin concentrations for the diagnosis of sepsis in critically ill neonates. Clin Infect Dis. 1998;26(3):664-672.
42. Reith HB, Mittelkötter U, Debus ES, Küssner C, Thiede A. Procalcitonin in early detection of postoperative complications. Dig Surg. 1998;15(3):260-265.

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