B·R·A·H·M·S PCT (Procalcitonin)

A Valuable Tool for

Sepsis Risk Assessment and Critical Care Management

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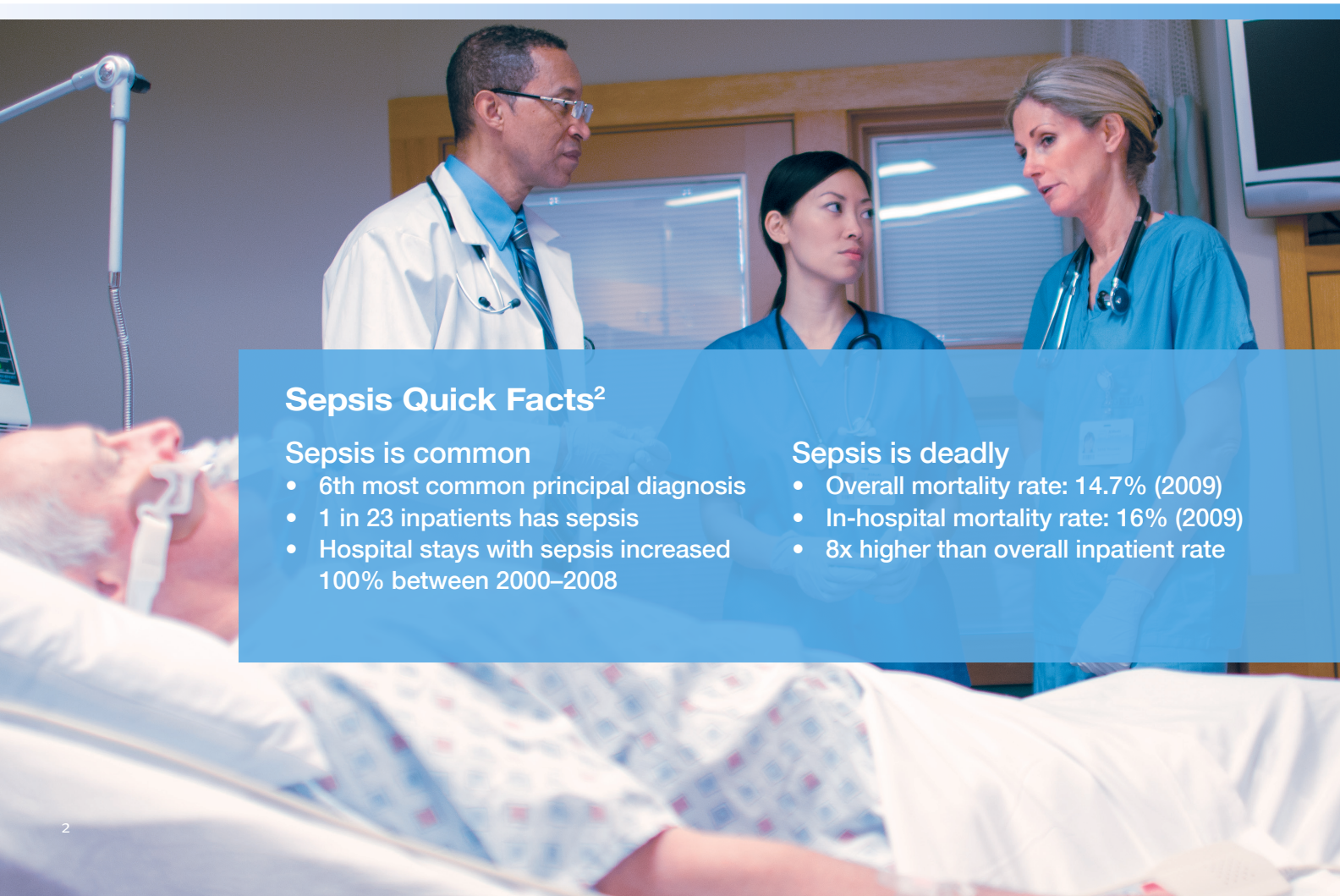
B·R·A·H·M·S PCT

New Insight for Sepsis Risk Assessment and Patient Management

Sepsis is a systemic inflammatory response to infection with some degree of organ dysfunction that can progress to organ failure and death.[1] It is the sixth most common principal diagnosis in the U.S. More than 1.6 million hospital stays are attributed to sepsis.[2] The mortality rate for sepsis is eight times higher than the overall inpatient mortality rate, resulting in 266,480 deaths annually (2009).[2] It is the most costly inpatient diagnosis, with aggregate annual hospital costs totaling $20.3 billion (2011).[3]

Early identification and intervention are crucial to improving sepsis outcomes.[4] However, this can be challenging due to the non-specific signs and symptoms associated with sepsis.



Sepsis Quick Facts[2]

Sepsis is common

- 6th most common principal diagnosis
- 1 in 23 inpatients has sepsis
- Hospital stays with sepsis increased 100% between 2000–2008

Sepsis is deadly

- Overall mortality rate: 14.7% (2009)
- In-hospital mortality rate: 16% (2009)
- 8x higher than overall inpatient rate

Assessing Risk Over Time

Thermo Scientific™ B·R·A·H·M·S PCT™ (Procalcitonin) provides clinicians in the intensive care unit, emergency department and hospital wards with a sensitive, specific STAT biomarker to aid in sepsis risk assessment for patients in or headed to the intensive care unit. In conjunction with other laboratory findings and clinical assessments, B·R·A·H·M·S PCT provides valuable information on the severity of a bacterial infection—both on presentation and during the course of treatment of the septic patient. The test takes just 20 minutes and results can therefore rapidly be made available for clinicians to support their decisions.

Aiding sepsis risk assessment

B·R·A·H·M·S PCT is a sensitive and specific biomarker of the inflammatory response to bacterial infection.[5] PCT levels above 2.0 ng/mL indicate a higher risk for progression to severe sepsis or septic shock.[6] PCT levels below 0.5 ng/mL indicate a low likelihood of progression to severe sepsis or septic shock.

This information can be obtained in emergency departments and hospital wards prior to admission to the intensive care unit to help determine both severity of illness and adequacy of source control. This initial PCT measurement provides a baseline for comparison with day 4 PCT values.

Aiding septic patient management

Following ICU admission, evaluating multiple B·R·A·H·M·S PCT measurements over consecutive days aids in assessing the response to empiric antibiotic therapy. As the infection is controlled, PCT will decline daily.[7] The Procalcitonin Monitoring Sepsis Study (MOSES) completed in the U.S. showed that sustained elevated PCT levels are an independent risk factor for mortality. PCT levels that decline less than 80% from the baseline within four days are associated with increased all-cause mortality—especially when the baseline PCT measurement is greater than 2.0 ng/mL.

Assessing PCT kinetics over time provides valuable information regarding patient disposition, response to treatment and likelihood of survival.

About the U.S. Multicenter MOSES Study[8]

The ability of B·R·A·H·M·S PCT to support mortality risk assessment over multiple days was demonstrated in a major multi-site U.S. study. The Procalcitonin Monitoring Sepsis Study (MOSES) included 858 adult patients with sepsis recruited across 13 investigational sites in the US.

Key findings of the study included:

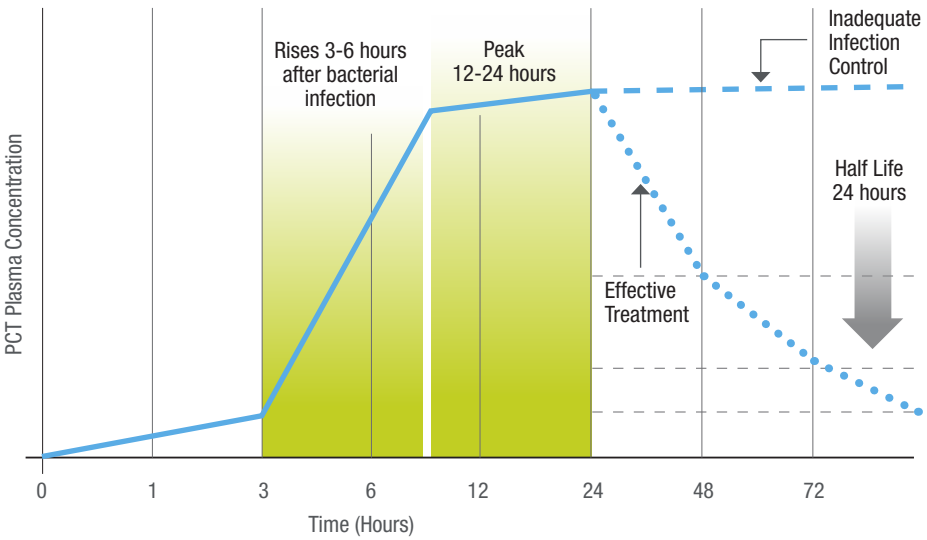
- The change of PCT over time aids in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock.
- A 2-fold increased risk of death is seen for patients showing a decrease in PCT less than or equal to 80 percent during the first four days following diagnosis of severe sepsis or septic shock compared to those who experienced a decrease in PCT greater than 80 percent. Mortality was the same for 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.

Understanding PCT Kinetics

The utility of B·R·A·H·M·S PCT as a tool for assessing sepsis and mortality risk stems from its unique kinetics in response to systemic bacterial infection.

When a bacterial infection occurs, PCT is one of a number of immunoactive molecules involved in the body's intrinsic immune response. In systemic bacterial infection, toll-like receptors flag the presence of microbial toxins. Inflammatory cytokines such as IL-1-ß, TNF-α, and IL-6 are simultaneously secreted from the cell. Signaling pathways then stimulate PCT transcription.[9,10] Since this local stimulation typically evolves over 3 to 6 hours, serum PCT levels may be low at this point.

Rapid and sustained response to bacterially induced systemic inflammation, and a half-life of 24 hours, are important hallmarks of PCT as a marker of sepsis risk.



If the pathogen is not contained, infection spreads and the body up-regulates proinflammatory mediators. As infection progresses and systemic inflammation intensifies, a dramatic increase in serum PCT occurs. This process continues for another 12 to 24 hours.[11]

It can take nearly 24 hours of appropriate antibiotic therapy to see reductions in serum PCT levels as the bacterial infection is controlled. PCT production and serum concentrations will decrease by up to 50% per day. However, if initial antibiotic therapy is inadequate, bacteria will continue to stimulate PCT production and blood levels will remain high.

During *viral* infections, PCT production is attenuated by interferon-γ that is released during the host response to the virus. Thus, PCT levels will not rise as they do in *bacterial* infections.

Interpreting PCT Results

Upon presentation

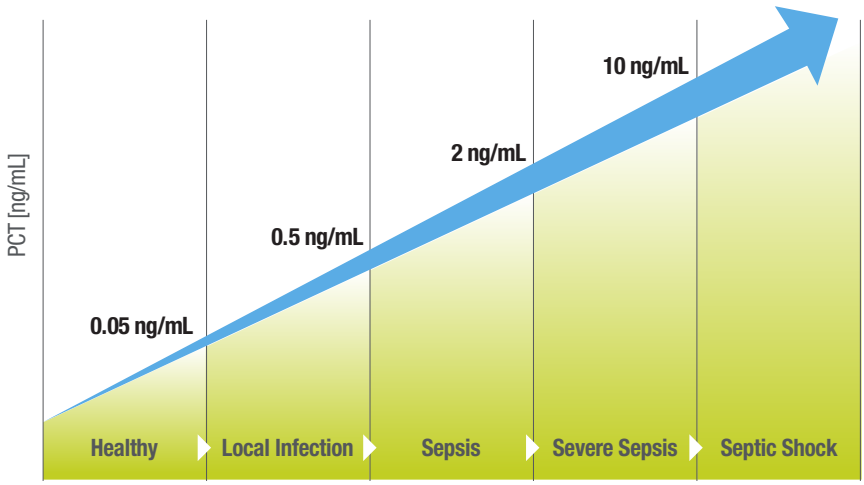
When using B·R·A·H·M·S PCT for initial assessment of sepsis risk on admission (Day 0), the following reference ranges of serum and plasma PCT concentrations should be considered.

PCT concentrations and sepsis risk [12,13,14]

- **Less than 0.5 ng/mL** – Low risk for progression to severe sepsis and/or septic shock
- **Between 0.5 and 2.0 ng/mL** – Sepsis should be considered
- **Greater than 2.0 ng/mL** – High risk for progression to severe sepsis and/or septic shock

PCT levels must always be interpreted in the context of other laboratory findings and clinical assessments.

PCT values rise in relation to sepsis severity, providing clinicians with a valuable tool for assessing patients suspected of sepsis.



Managing care

When using B·R·A·H·M·S 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%** – 2-fold higher risk of all-cause 28-day mortality
- **Baseline PCT measurement less than or equal to 2.0 ng/mL or greater than 2.0 ng/mL** – Additional information about the mortality risk when evaluating the patient's clinical course with PCT measurements on subsequent days.

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

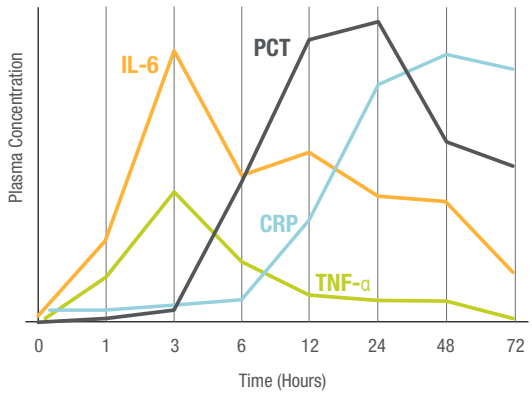
Comparing PCT to Other Biomarkers

The sensitivity and specificity of PCT to 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.

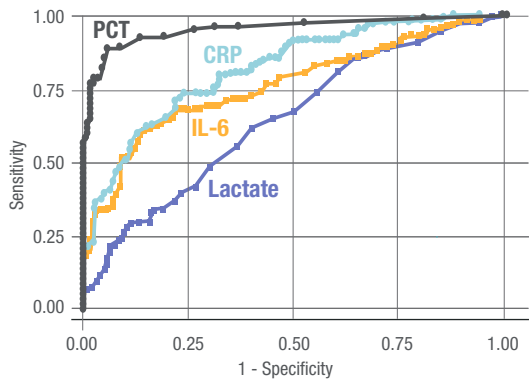
Lactate

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.[16] However, lactate is not specific for bacterial infection. Clinical conditions including microcirculatory dysfunction, shunting, regional blood flow maldistribution, exaggerated aerobic or anaerobic glycolysis, hypovolemia or arterial hypotension can increase lactate levels.[17] In addition, lactate does not rise until late in the course of sepsis.[18]

The unique kinetics of PCT make it a valuable complement to other biomarkers of sepsis.



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.



C-Reactive Protein (CRP) and IL-6

CRP secretion is triggered by cytokines (IL-6, IL-1-ß, 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.[19,20,21] 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.[15]

IL-6 is produced in response to tumor necrosis factor alpha (TNF-α), and induces synthesis of CRP. Serum levels of IL-6 rise within one hour of inflammation and decline quickly, increasing the risk for false negative results when drawn as the patient exhibits signs of sepsis.[22]

PCT levels steadily increase over 12 hours and can be detected sooner than CRP, allowing early assessment. Unlike cytokines, PCT's unique kinetics help clinicians detect sepsis over a much wider time window than IL-1-ß, TNF-α, and IL-6.[23]

Blood Cultures

Despite recent advances, blood cultures often lack the sensitivity to identify the infecting pathogen in severe sepsis and septic shock. The delay in results due to slow-growing organisms and decreased sensitivity in patients already receiving antibiotics can be challenging. Only 30-40% of patients with a clinical diagnosis of severe sepsis or septic shock have positive blood cultures.[24]

Important Considerations When Interpreting PCT Results

The prognostic value of PCT in the setting of sepsis has not been validated in US patients younger than 18.

Increased PCT levels may not always be related to systemic bacterial infection.[14,25,26,27] 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 first two days of life

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. In cases where the laboratory results do not agree with the clinical picture or history, additional tests should be performed. Refer to Thermo Scientific B·R·A·H·M·S PCT package insert for additional information.

B·R·A·H·M·S PCT: The Quality Standard

When using PCT assays to support clinical decisions, quality and experience count. Clinicians in health systems worldwide have relied on B·R·A·H·M·S PCT since 1996 to make patient care decisions with confidence.

More than 3000 publications in both the U.S. and Europe have demonstrated the clinical utility of PCT and defined clinical cut-offs and treatment algorithms based on the B·R·A·H·M·S PCT assay performance.

The Procalcitonin Monitoring Sepsis Study (MOSES) expands the clinical utility of B·R·A·H·M·S PCT to include mortality risk assessment to help gauge infection response to treatment. B·R·A·H·M·S PCT stands for quality and clinical confidence.

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