ARUP LABORATORIES

Procalcitonin (PCT)

FOR DIAGNOSIS OF BACTERIAL INFECTION AND SEPSIS

Test Highlights

- Provides early evaluation of patient risk for developing sepsis.
- Differentiates between bacterial infection and other causes of inflammatory reaction.
- Serum levels correspond to severity of infection and response to treatment.
- BRAHMS PCT sensitive KRYPTOR assay has improved sensitivity and measurement range (0.06 ng/mL−5,000 ng/mL) compared to other formats of procalcitonin measurement.

Clinical Background

- Identifying patients with bacterial infection and sepsis is a major challenge in emergency departments and critical care units, where mortality from sepsis remains high due to delayed diagnosis and treatment. The traditional clinical signs of infection and routine laboratory tests used to diagnose bacterial infection and sepsis (e.g., C-reactive protein, WBC, or lactate) lack diagnostic accuracy and can be misleading.
- Procalcitonin (PCT) is a protein that can act as a hormone and a cytokine. It can be produced by several cell types and many organs in response to pro-inflammatory stimuli, particularly bacterial infection. It is released under the stimulation of sepsis.
- PCT levels rise within six–12 hours of bacterial infection with systemic consequences. In patients with sepsis, severe sepsis, and septic shock, PCT levels can reach 1,000 ng/mL. Once the bacterial infection is resolved, PCT levels rapidly decrease.
- A large database of literature and clinical experience is available for PCT, and several tests are now FDA-cleared.

Indications for Ordering

- The PCT test has been cleared by the FDA for use with critically-ill patients on their first day of ICU admission, as an aid in determining their risk of developing severe sepsis and septic shock.
- The 2008 guidelines for evaluation of new fever in adult ICU patients, as established by the American College of Critical Care Medicine and the Infectious Disease Society of America, state that: “Serum procalcitonin levels and endotoxin activity assay can be employed as an adjunctive diagnostic tool for discriminating infection as the cause for fever or sepsis presentations (level 2).”

Interpretation of Results

- PCT concentrations in healthy individuals: < 0.1 ng/mL
- Published data supports the following interpretative risk assessment criteria:
  - PCT > 2 ng/ml: PCT levels above 2.0 ng/mL on the first day of admission indicate a high risk of progression to severe sepsis and/or septic shock.
  - PCT < 0.5 ng/ml: PCT levels below 0.5 ng /mL on the first day of admission indicate a low risk of progression to severe sepsis and/or septic shock.
- PCT levels less than 0.5 ng/mL do not exclude infection. Localized infections (without systemic signs) may also be associated with low levels.
- If PCT levels are measured soon after the systemic infection process has started (usually less than six hours), values may still be low.
- Various noninfectious conditions are known to induce PCT. Levels between 0.5 ng/mL and 2.0 ng/mL should be reviewed carefully, taking into account the clinical background and condition of the individual patient.

Limitations

- Increased PCT levels may not always be related to systemic infection.
- Noninfectious conditions that may increase PCT levels include:
  - Major trauma, surgical trauma (including extracorporeal circulation), and burns.
  - Neonate (first two days of life).
  - Medullary C-cell carcinoma, small cell lung carcinoma, or bronchial carcinoid.
  - Treatment with OKT3 antibodies, interleukins, TNF-α, and other drugs stimulating the release of pro-inflammatory cytokines.
  - Prolonged or severe cardiogenic shock, prolonged severe perfusion anomalies, Child-Pugh Class C liver cirrhosis, and peritoneal dialysis treatment.
- Results of the PCT assay should be evaluated within the context of other laboratory findings and the clinical status of the patient.
- A hook effect has been reported at PCT concentrations > 2500 ng/mL. If clinical presentation and/or previous results are inconsistent with reported results, then retesting with a dilution should be requested.

Methodology

- Immunofluorescence (homogeneous sandwich immunoassay).
- Measuring principle based on Time-Resolved Amplified Cryptate Emission (TRACE®) technology, which measures the signal from an immunocomplex with time delay.

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References

1. Christ-Crain M and Muller B. Biomarkers in respiratory tract infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. European Respiratory Journal 2007;30:3.
2. Christ-Crain M., et al. Procalcitonin in bacterial infections-hype, hope, more or less? Swiss Med Wkly 2005;135:451–460
3. Jensen. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. Crit Care Med 2006;34:10.
4. Stoltz D, et al. Antibiotic Treatment of Exacerbations of COPD. CHEST 2007;131:1.
5. BRAHMS PCT sensitive Kryptor® Instruction Manual (Version 2.0us) April 2007.
6. O'Grady, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. Crit Care Med 2008;36:1330–1349.

Test Information

0020763 Procalcitonin

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.

Dr. Charles Hawker and the Discovery of Procalcitonin

Charles D. Hawker, PhD, MBA, FACB, currently serves as scientific director of automation and special projects at ARUP Laboratories, as well as a Professor of Pathology (Adjunct) at the University of Utah School of Medicine. Before Dr. Hawker came to ARUP, he was involved in the discovery of the role of procalcitonin in diagnosing and monitoring septic shock.

Around 1980, Dr. Hawker's laboratory (the Laboratory Procedures Esoteric Center at the Upjohn Company, Kalamazoo, Michigan) had one of the few radioimmunoassays for calcitonin in the United States. Dr. Hawker was contacted by Dr. Russell W. Chesney, an endocrinologist at the University of Wisconsin (Madison), who indicated that many patients with toxic shock syndrome were experiencing lowered serum calciums that could not be explained. [This was before Medicare had prohibited multi-test panels; 27-test profiles that included serum calcium were frequently ordered when lab work was needed]. Dr. Hawker agreed to run calcitonin (CT) levels on specimens from some of these patients as a possible explanation for the hypocalcemia.

All of the serum specimens subsequently tested had significantly elevated immunoreactive calcitonin values, with some being more than 100 times the upper reference limit and similar to levels seen in patients with medullary thyroid carcinoma (MTC). Dr. Hawker and a scientist in his laboratory, Dr. Francis P. DiBella, then carried out further research to determine whether the calcitonin in these patients was authentic calcitonin or some other form that was cross-reacting in the radioimmunoassay. They performed gel filtration studies to compare the elution profile of the calcitonin immunoreactivity in the serum of a patient with toxic shock syndrome to the elution profile of the calcitonin immunoreactivity in a patient with MTC producing similarly excessive amounts of calcitonin.

Because the form of calcitonin that eluted from the serum of the patient with toxic shock syndrome appeared much larger in size than authentic (intact) calcitonin, it was thought to have been a polymeric form. [At the time of these studies, the concept of prohormones had only been discovered for a few hormones, and calcitonin was not one of those]. In order to learn more about this potentially larger form of calcitonin, Drs. Hawker and DiBella performed the gel filtration studies before and after treatment of the patient serum specimens with 2-mercaptoethanol, a reducing agent that breaks disulfide bonds, which might disrupt a polymeric form. There was no change in the size of the authentic calcitonin from the patient with medullary thyroid carcinoma that eluted from the gel filtration column, but the 2-mercaptoethanol shifted the calcitonin immunoreactivity measured after gel filtration from the larger, perhaps polymeric, form of calcitonin to a somewhat smaller form that was still larger in size than authentic calcitonin.

This research was published in 1983 in the Journal of Laboratory and Clinical Medicine.[1] The authors included Drs. Chesney, Hawker, and DiBella, along with two well known endocrinologists, Dr. John Haddad of the University of Pennsylvania (a former President of the American Society for Bone and Mineral Research), and Dr. David McCarron of the University of Oregon, both of whom had also seen patients with toxic shock syndrome and lowered serum calcium levels. Two other physicians at the University of Wisconsin, Dr. Joan Chesney and Dr. Jeffrey Davis, were also included as authors of this publication.

An important 2004 review article on procalcitonin (CTpr) and sepsis[2] stated : "An initial publication in 1983 first called attention to increased serum levels of immunoreactive CT in patients with the staphylococcal toxic shock syndrome, a severe form of sepsis." The authors then credited the early research conducted by Dr. Hawker and his colleagues with providing "…the inspiration for multiple subsequent studies of CTpr in inflammation, systemic infection, and sepsis." In this review, the authors noted that the two larger forms identified in the early report were likely procalcitonin and the 21-amino acid CT carboxyterminus peptide I (CCP-I), another CT precursor.

For more information on procalcitonin, including a video lecture, please visit http://arup.utah.edu/education/procalcitonin.php.

References

1. Chesney RW, et al. Pathogenic mechanisms of the hypocalcemia of the staphylococcal toxic-shock syndrome. J Lab Clin Med 101(4): 576-585, 1983.
2. Becker KL, et al. 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 89 (4): 1512-1525, 2004.