EDUCATIONAL COMMENTARY – PROCALCITONIN

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Learning Outcomes
Upon completion of this exercise, the participant will be able to:

- list and discuss the stages in the progression from bacterial infection to septic shock
- describe the use of procalcitonin as a marker of sepsis
- interpret procalcitonin levels

Sepsis
The incidence of sepsis in the United States is approximately 750,000 cases per year. Sepsis and septic shock are the leading causes of death in intensive care units. Sepsis is not a specific disease but is the systemic inflammatory response to bacterial, viral, fungal, or parasitic infection. In 1992, a consensus statement of the American College of Chest Physicians and the Society of Critical Care Medicine stated that the initial systemic inflammatory response (SIRS) to infection required two or more of the following criteria:

- temperature of less than 36ºC or greater than 38ºC
- heart rate greater than 90/minute
- respiratory rate greater than 20/minute or a P CO2 result of less than 32 mmHg
- white blood cell count greater than 12,000/µL or less than 4000/µL

Sepsis was defined as documented infection with two or more SIRS criteria. When SIRS affects one or more vital organs, severe sepsis occurs. Septic shock was defined as sepsis with nonresponsive hypotension and perfusion abnormalities. Mortality in patients with septic shock approaches 60%, but studies show that early diagnosis and treatment can improve mortality rates. Diagnosis of sepsis is difficult because the clinical signs and symptoms (which may include chills, fever, nausea, rapid breathing, rapid heartbeat, confusion, and decreased urine output) are nonspecific. Most cases of sepsis are due to bacterial or fungal infection, and early diagnosis facilitates initiation of appropriate therapy. Effective treatment and prognostic assessment can be enhanced by differentiation of bacterial infection from other types of infection.

Laboratory Detection of Sepsis
Current guidelines recommend culture for all patients suspected of having sepsis although results of as many as 50% of cultures in patients who have severe sepsis or septic shock may be negative. Treatment is delayed for 24 hours or longer awaiting culture results. Traditional markers of inflammation such as the C-reactive protein level or the white blood cell count have low sensitivity and specificity for detection of bacterial infection. Discovery of an ideal serum marker for sepsis has focused on compounds specific for
the systemic inflammation resulting from bacterial infection. Proinflammatory cytokines such as tumor necrosis factor alpha (TNF alpha), interleukin 1 beta (IL-1β), and interleukin 6 (IL-6) have been used, but they also lack specificity. At least 34 potential serum biomarkers for diagnosis of sepsis have been studied, and procalcitonin (PCT) has emerged as a leading candidate for early detection of bacterial infection.

**Procalcitonin**

PCT is a 116-amino-acid polypeptide produced in healthy individuals by the C-cells of the thyroid and to a small extent by neuroendocrine tissue of other organs, such as lungs and intestines. Normally PCT concentrations in blood are very low because it is a prohormone that is converted to the calcium regulatory hormone calcitonin in the thyroid. Neuroendocrine tumors, including medullary thyroid cancer, small cell lung cancer, and carcinoid tumors, produce PCT, but they convert it to calcitonin prior to release into the blood. Stressors such as systemic bacterial infection stimulate production of PCT by other cells in the body. Unlike thyroid C-cells and tumor cells, these cells cannot modify PCT to produce calcitonin, so high concentrations of procalcitonin and not calcitonin are observed in patients with systemic inflammation and sepsis. In a person with sepsis, PCT levels increase within 2 to 4 hours, reach peak concentrations in 8 to 24 hours, and remain elevated as long as the inflammatory process continues. The exact role of PCT in sepsis is unknown. The half-life of PCT is 25 to 30 hours, which allows for its use in monitoring response to antibiotics. Other stressors that can cause PCT elevation include infection from other causes and tissue damage due to trauma, surgery, pancreatitis, burns, or cardiogenic shock. PCT levels are also elevated in other conditions, including adrenal failure, acute organ transplant rejection, transplant patients receiving pan T-cell antibody therapy, and patients scheduled for hematopoietic stem cell transplantation receiving anti-thymocyte globulin.

**Interpretation**

Plasma PCT concentrations in healthy individuals are typically less than 0.05 ng/mL but can be as high as 1000 ng/mL in patients with severe sepsis or septic shock. Not all patients with severe sepsis have elevated PCT levels, and not every patient with an elevated level of PCT has sepsis, but as a group patients with sepsis have higher serum PCT levels. Although different cutoff levels have been used, most studies use a value of 2.0 ng/mL or higher as the threshold for the diagnosis of a high risk of sepsis and an indication to initiate antibiotic and other specific therapy. PCT levels of less than 0.5 ng/mL are considered indicative of low risk of sepsis, and values between 0.5 ng/mL and 2.0 ng/mL are considered indicative of an uncertain risk. Recommendations for patients with concentrations in the indeterminate range include recollection and remeasurement as well as consideration of other causes of elevated PCT level. There is some consensus that in patients with infection, PCT concentrations of less than 0.1 ng/mL are highly suggestive of a nonbacterial etiology. Some advocates of PCT-guided antibiotic treatment recommend initiation of treatment at levels as low as 0.25 ng/mL.
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Assays
The US Food and Drug Administration (FDA) has approved some PCT devices (combinations of assays and instruments) with indication of use being “to aid in the assessment of risk progression to severe sepsis and septic shock in critically ill ICU patients on the first day of admission.” When used in conjunction with other laboratory findings and clinical assessments, these devices help determine whether an infection is bacterial or viral and thus aid in avoidance of unnecessary use of antibiotics. In 1996, Brahms Diagnostica (Berlin, Germany) marketed the first PCT assay in Europe, and in 2005, the company received FDA clearance for the BRAHMS PCT LIA (Brahms Diagnostica, Tracys Landing, MD), a manual immunochemistry method. Since then methods suitable for use on automated platforms have been cleared by the FDA. These include the Brahms PCT Kryptor (Brahms USA, Annapolis, MD) and the Vidas Brahms PCT (bioMerieux, Hazelwood, MO). Roche Diagnostics (Indianapolis, IN), Siemens Medical Solutions (Tarrytown, NY), and other companies have PCT assays on automated platforms under development or in the process of seeking FDA approval. Sensitivity and precision at low concentrations are critical analytic parameters for PCT assays because of the low levels in healthy individuals and the desire to detect even slightly elevated levels and changes for diagnosis of risk and monitoring of treatment.

Conclusions
Clinical studies have resulted in mixed results and conclusions concerning the use of the PCT level as a marker of sepsis and to guide antibiotic therapy. The authors of a meta-analysis of 18 studies concluded that PCT cannot reliably differentiate between sepsis and SIRS. Another meta-analysis of 7 randomized controlled trials using PCT-guided antibiotic therapy in the intensive-care unit concluded that such therapy may reduce antibiotic exposure without compromising clinical outcomes but that further research is necessary before wide adoption of the strategy. Several other studies have been performed since the publication of these reviews, and clinical use of PCT has increased. The Agency for Healthcare Research and Quality has recognized the need for a systematic review of the use of PCT and has proposed such a project entitled: Comparative Effectiveness of Procalcitonin-Guided Decisions for the Diagnosis and Management of Sepsis. Hopefully this project will answer some of the questions currently being asked about the use of PCT in the risk assessment and antibiotic therapy of sepsis due to bacterial infection.
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References


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