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Procalcitonin in Sepsis

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Introduction:

Sepsis is defined as the confirmed or likely presence of infection in combination with systemic manifestations of infection¹. Unfortunately, cultures may be negative and systemic manifestations (also known as systemic inflammatory response syndrome or SIRS) can also result from a noninfectious etiology. Because delays in diagnosis and treatment of sepsis increase mortality, we need reliable diagnostic biomarkers to identify early sepsis². Procalcitonin (PCT) has been studied over the past two decades as a potential marker for bacterial infections.

PCT is the 166-amino-acid precursor of calcitonin that is produced by the C-cells of the thyroid gland and is cleaved into calcitonin, katacalcin, and an N-terminal fragment. PCT levels are undetectable (< 0.1 ng/ml) in otherwise healthy adults. In bacterial sepsis, PCT levels increase rapidly secondary to its synthesis from almost all parenchymal tissues which lack the ability to cleave PCT^{3,4}. In contrast, viral infections or noninfectious inflammatory reactions do not or only result in a moderate increase in PCT levels in blood. Moreover, recovery from bacterial infection with antibiotic therapy, resulted in a simultaneous decline in PCT levels⁵. Hence, PCT has been used as a diagnostic and prognostic biomarker in sepsis. Over the years, the role of PCT has expanded to aid in antibiotic stewardship programs to curtail the use of unnecessary antibiotics for noninfectious SIRS or viral infections⁶.

Procalcitonin measurement:

PCT is detectable in blood within 2-4 hours of infection, peaks within 6-24 hours and can be present for up to 7 days. The half-life is 22-26 h. All PCT assays are based on immunoassay techniques⁴. There are no studies precisely defining the optimum time for PCT measurement and it is unclear whether trends or absolute levels should be used. The cutoffs that separated patients with sepsis from those without sepsis have varied greatly between studies². Changes in the cutoff values alter the sensitivity at the cost of specificity or vice versa. The figure below shows a comment attached to a reported PCT value in our facility (VIDAS® B.R.A.H.M.S. PCT™, bioMérieux, Durham, NC).

PCT ≤ 0.5 ng/mL Systemic infection (sepsis) is not likely. Local bacterial infection is possible

PCT > 0.5 and <+ 2 ng/mL Systemic infection (sepsis) is possible, but other conditions are known to elevate PCT as well.

PCT > 2 ng/mL Systemic infection (sepsis) is likely, unless other causes are known.

PCT ≥ 10 ng/mL Important systemic inflammatory response, almost exclusively due to severe bacterial sepsis or septic shock

Figure 1: Comments attached to the procalcitonin (PCT) report in our institution.

Procalcitonin as a diagnostic biomarker:

Early administration of empiric or appropriate antibiotic therapy is indicated in sepsis. At the same time, being able to hold or stop antibiotics in noninfectious SIRS is also important to reduce antibiotic costs, side effects and bacterial resistance. Hence, it is important to distinguish sepsis from noninfectious SIRS in the intensive care unit. The 2012 International Guidelines for the Management of Severe Sepsis and Shock, clarify that PCT levels or other biomarkers such as C-reactive protein (CRP) do not help to differentiate the acute inflammation of sepsis from other causes of generalized inflammation¹. However, the same guidelines connote that low PCT levels can assist the decision to discontinue empiric antibiotics in cases where sepsis was included in the initial differential diagnoses at admission, but had no subsequent evidence for infection.

Several meta-analyses have investigated the accuracy of PCT for the diagnosis of sepsis, with conflicting results. Uzzan et al. found that PCT represented a good biological diagnostic marker for sepsis, severe sepsis, or septic shock in critically ill patients and PCT fared better than CRP for identifying sepsis⁷. In contrast, Tang et al. reported a low diagnostic performance of PCT with both sensitivity and specificity being 71% (95% CI 67-76)⁸. Major limitations in both meta-analyses were non-inclusion of a heterogeneous patient population and bias generated by the choice of definition for sepsis which does not have a universally accepted gold standard definition to-date. Wacker et al. performed a meta-analysis with the intention of addressing these limitations. Of the 3,244 critically ill patients, 1,863 (57%) had sepsis and 1,381 (43%) had SIRS of noninfectious origin. Pooled sensitivity was 0.77 (95% CI 0.72-0.81) and specificity was 0.79 (95% CI 0.74-0.84). The area under the receiver operating characteristic curve was 0.85 (95% CI 0.81-0.88). The authors concluded that PCT may be a helpful marker for early diagnosis of sepsis in critically ill patients, particularly if used in the context of medical history, physical examination, and microbiological assessment.²

Procalcitonin as a prognostic biomarker:

In community-acquired pneumonia and ventilator-associated pneumonia, PCT was shown to predict risk of death^{9, 10}. Procalcitonin levels in the early stages of sepsis are significantly lower among survivors versus non-survivors of sepsis¹¹. A study in adults admitted to intensive care units with SIRS, reported that PCT level decreased significantly from day 1 to day 2 in survivors but not in nonsurvivors, suggesting that serial measurements improve its accuracy for mortality prediction¹². Liu et al. recently published a meta-analysis including 3,994 patients and found that PCT non-clearance was associated with an increased risk of death in patients with sepsis. Even in early studies on PCT, where patients were categorized into SIRS, sepsis, severe sepsis and septic shock, PCT levels were more elevated in patients with severe sepsis and septic shock³.

Procalcitonin in antibiotic stewardship:

Antibiotic stewardship programs (ASP) in several hospitals have included procalcitonin into their algorithms in order to appropriately start or stop antibiotics. One study evaluated usefulness of PCT for the initiation of antibiotic in intensive care unit patients but found it to be not useful¹³. A prospective randomized controlled trial compared a PCT-guided

antibiotic regimen to a standard antibiotic regimen in surgical intensive care patients; in the PCT group, antibiotics were discontinued if clinical findings of infection improved and PCT levels decreased to less than 1 ng/ml or had dropped to 25-35% of the initial value over three days if the PCT level remains above 1 ng/mL. The duration of antibiotic therapy was significantly shorter in the PCT group than in the control group (5.9 +/- 1.7 versus 7.9 +/- 0.5 days, <0.001)¹⁴. One program was able to decrease antibiotic consumption by 21.2% a year after implementation of a PCT-guided ASP¹⁵; however, mortality rate and length of stay remained unchanged over the study period. Schuetz et al. proposed adapted algorithms based on 14 randomized controlled trials that investigated procalcitonin protocols for antibiotic treatment decisions in adult patients with respiratory tract infections and sepsis from primary care, emergency department, and intensive care unit settings¹⁶. For example, for the intensive care unit, the investigators proposed that antibiotics should be discouraged if the PCT was <0.5 ng/ml and strongly discouraged if the PCT was <0.25 ng/ml but this could be overruled if there is clinical suspicion of infection. If antibiotics were started for suspected sepsis in the intensive care unit, PCT levels can be monitored from initiation of antibiotic therapy, and if PCT levels decline to <0.5 ng/ml or drop by 80%, cessation of antibiotics can be considered. They concluded that PCT measurement appears to reduce antibiotic exposure without worsening the mortality rate.

Conclusion:

PCT is not a perfect marker for a diagnosis of sepsis. Nevertheless, it could be very helpful in addition to a thorough history, physical exam, appropriate laboratory tests and imaging. Sensitivity and specificity varied according to the cutoffs used, but specificity increases as the value rises. Persistent PCT elevation over days may prognosticate increasing severity of illness and mortality. A value of less than < 0.5 ng/ml in a patient with SIRS without the evidence of infection and negative cultures, can be used to support the clinician's decision to discontinue antibiotics. Clinical judgement is always required when using this biomarker.

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