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Procalcitonin in neonatal sepsis

Pathology

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ABSTRACT

The differentiation of sepsis and systemic bacterial infections from other causes of systemic inflammatory response is crucial from the therapeutic point of view. The clinical signs and symptoms are non-specific and traditional biomarkers like white cell count, erythrocyte sedimentation rate and C-reactive protein are not sufficiently sensitive or specific to guide therapeutic decisions. Procalcitonin (PCT) is considered a reliable marker for the diagnosis and prognosis of moderate to severe bacterial infections, and it has also been evaluated to guide the clinicians in the rational usage of antibiotics. This review describes the diagnostic and prognostic role of PCT as a biomarker in various clinical settings.

INTRODUCTION

Features of an ideal sepsis marker are,Easy to use, interpret, reproducible, high sensitivity and specificity, should show rapid increase and decrease , show appropriate response with effective therapy , co-relate with disease severity, cheap. Name suggests, it is a precursor of calcitonin, produced by the C-cells of thyroid under the control of the calcitonin gene related peptide 1 *(CALC-1)* gene. Normally, the expression of the gene is found in the neuroendocrine cells of the thyroid and the lung. However, during microbial infections there is increased *CALC-1* gene expression in various extra-thyroid tissues and cells including kidneys, liver, pancreas, leucocytes, and adipose tissue with concomitant release of PCT throughout the body. The normal physiological level of PCT in serum is less than 0.1ng/mL which can increase several folds in systemic bacterial infections.

The pathophysiological role of PCT in sepsis is imperfectly understood. It has been proposed that in inflammation, the release of PCT may be a two way process: direct and indirect. The toxins and lipopolysaccharides released by microbes can induce the release of PCT in a direct manner; or alternately the inflammatory cytokines likinterleukin (IL) 1b,IL-6, tumour necrosis factor- (TNF) etc may indirectly influence PCT production. IFN released in response to viral infection can cause a down-regulation of PCT. This makes PCT a more specific marker for bacterial infection.

Thus, during severe bacterial infections, the level of PCT may rise several hundred-folds and may even reach a level of 1000 ng/mL without any change in serum calcitonin level. However, it is important to keep in mind the following situations while interpreting PCT reports: (I) Gram negative bacteraemias cause higher elevation of PCT than those caused by Gram positive pathogens; (ii) there is a low or negligible rise in PCT levels in localized infections, and in infections caused by viruses or intracellular bacteria; and (iii) in the neonatal period, particularly in the first 48-72 hours of life, serum PCT levels increase to a high level and then gradually fall during the first week. This is possibly due to initial establishment of gut flora

MATERIAL AND METHODS

Reader is a **fluorescence scanning instrument** used in conjunction with QDx InstacheckTM Immunoassay Tests which are based on antigen-antibody reaction and fluorescence technology. Reader uses a semiconductor diode laser as the **excitation light source for illuminating the test cartridge membrane** specimen duly processed) thereby triggering fluorescence from the fluorochrome molecules present on the membrane.

The fluorescent light is collected together with the scattered laser light. Pure fluorescence is filtered from the mixture of the scattered and fluoresced light.

Intensity of the fluorescence is scanned and converted into an electric signal which is proportional to the intensity of fluorescence produced on the test cartridge membrane.

The on-board microprocessor computes concentration of the analyte in the clinical specimen based on **a pre-programmed calibration.** The computed and converted result is display Serum sample is needed for the test.

RESULT

A systematic review which included studies on infections among the newborns (up to 28 days age) found that PCT was a useful diagnostic marker in early stages of bacterial infections (sensitivity= 87%, specificity=82% at a cut off value of 8 ng/mL) compared to CRP (sensitivity= 64%, specificity=80%, cut off value of 10 mg/L). However, it should be noted that there is a surge of PCT in the first 24-48 hours of life which returns to normal over the next 3-7 days. In older children with more invasive bacterial infections like sepsis and meningitis, levels of PCT were significantly higher compared to CRP; and moreover during the period of evolution of fever (<8 hours), PCT performed better than CRP with a more rapid rise in its level. Another study which involved children with bacterial and viral pneumonia revealed that on admission 100% of the children with bacterial pneumonia had high levels of PCT (0.94- 6210 ng/mL), while only 34% of the children with viral pneumonia had PCT levels between 0.5-2.13 ng/mL. In this study, it was concluded that PCT concentration of greater than 2.0 ng/mL had 100% sensitivity, 98% specificity, and a positive predictive value of 93% for bacterial pneumonia. CRP levels were elevated in 100% and 88% cases of bacterial and viral pneumonia respectively, giving a specificity of 38% and positive predictive value of 42% for bacterial pneumonia.

Causes of false-positive and false-negative PCT results

False positive Results

Neonates <48 hrs age,First days after major surgery, trauma, burn,Treatment with OKT3 antibodies, interleukins, TNF- Invasive fungal infections, acute attack of falciparum malaria Prolonged or severe cardiogenic shock

Malignancies: e.g., medullary C-cell carcinoma of thyroid, small cell cancer of lung, bronchial carcinoid

False negative results

Early course of infection,Localized infections,Sub acute bacterial endocarditis

Reference Interpretation values (ng/mL)

<0.05 Normal

<0.5 Localized infection possible. Re-test after 6-24 hours

 0.5-<2 Systemic bacterial infection possible. Re-test after 6-24 hours

 2-<10 Systemic bacterial infection is likely. High risk for severe sepsis

 10 Severe bacterial sepsis, septic shock

CONCLUSION

Serum PCT levels appears to be a significant improvement over CRP

Thus a point-of-care rapid test which can provide prognostic information can be very useful for the clinician in decision making regarding early intervention. PCT may be helpful to assess the severity of the infection. The favourable kinetic profile of PCT makes it a useful clinical marker. PCT promptly increases within 6-12 hours after an infection trigger and the levels halve daily when the infection is controlled. A decrease in PCT level by more than 30% after the first 24 hrs from the onset of antimicrobial therapy is indication of appropriate treatment and control of infection. PCT thus, appears to be promising as a bio marker for diagnosis and prognosis of moderate to severe bacterial infections and as a guide for antibiotic therapy. Further studies in field-conditions from tropical countries may help in establishing PCT as a point-of-care diagnostic test. The other potential bio markers need additional studies using larger number of patients before their use can be validated. The scenario which is emerging seems to suggest that any single bio marker is unlikely to identify and stratify all patients adequately, and a combination of such markers may reveal a clearer picture.