Bacterial infections are a major cause of mortality and morbidity. Early diagnosis of infection is crucial, but remains a challenge to the treating clinician. The use of diagnostic tests is challenging because the clinical presentations of systemic inflammatory response syndrome (SIRS) and sepsis may be similar despite differing aetiologies. Treatment of bacterial infections with antibiotics is not only ineffective, but contributes to the development of antibiotic resistance, increased medical costs and drug toxicity which may increase the morbidity and mortality in already compromised patients. Cultures are the most precise way to diagnose infection, these take time to yield results. The routine use of a reactive marker of infection to help guide treatment and reduce misuse of antibiotics is necessary in today’s antibiotic-resistant climate. A number of biological markers are currently in use to address this need, amongst these are procalcitonin and C-reactive protein.}

**PROCALCITONIN (PCT)**

PCT is a prohormone of calcitonin. It is produced by the C-cells of the thyroid and is primarily responsive to inflammation and hypercalcaemia. Under this circumstance, negligible concentrations are produced. During sepsis/inflammation parathyroid cells produce large amounts, modulated by lipopolysaccharides and cytokines. The major mature form, PCT-19 and T-27, PCT is a mediator of the immune response. It acts as a chemokine influencing migration of monocytes, granulocytes and macrophages to inflammation sites. It therefore plays a regulatory function during infection. As a marker, PCT is well established. PCT secretion starts 4 hours post stimulation and peaks at 8 hours. It has a half-life of between 20-36 hours and clears within a few days. PCT is measured quantitatively or semi-quantitatively in serum or plasma by immunoassay. The result is provided as a quantitative or semi-quantitative value. The conversion to a percentage is done by a software attached. The measuring range is 0.02 – 100ng/ml depending on the assay used.

**Uses**

1. **Diagnosis of bacteremia and septicaemia in adults and children (including neonates especially >72 hours post birth)**
2. **Diagnosis of renal involvement with paediatric and chronic kidney disease**
3. **Diagnosis of bacterial infection in neonatal patients**
4. **Outlook, risk stratification and monitoring of septic shock**
5. **Assessing progression and progression in sepsis and SIRS**
6. **Diagnosis of bacterial versus viral meningitis**
7. **Diagnosis of community-onset acquired bacterial versus viral pneumonia**
8. **To guide decisions on when to initiate antibiotic therapy**
9. **Monitoring of therapeutic response to antibiotic therapy**

**Interpretation of results**

- **0.5ng/ml represents a low risk of severe sepsis and/or septic shock**
- **2ng/ml represents a high risk for severe sepsis and/or septic shock**

**General considerations**

- In children ≥72 hours old and in adults, levels <0.5 ng/ml, make a diagnosis of significant bacterial infection unlikely.
- Mild elevations between 0.5-2ng/ml, and 2-5ng/ml, are consistent with localized, mild-to-moderate bacterial infection. These levels can also be seen in patients, with non-bacterial SIRS.
- Levels above 2.0ng/ml, are highly suggestive of a systemic bacterial infection/sepsis or severe localized bacterial infection, such as severe pneumonia, meningitis, or peritonitis. In cases of non-bacterial elevations, levels should begin to decrease after 24-48 hours.
- Autoimmune diseases, chronic inflammatory processes, viral infections and mild localized infections rarely lead to elevations of PCT ≥ 0.5ng/ml.

**Specific diagnostic applications, based on the current literature**

- **Diagnosis of bacteremia and septicaemia in adults and children**
- **Assessment of treatment of bacterial infections with antibiotics**
- **Prognostic value in most studies as for mortality**

**PCT levels that are elevated in non-infective, severe inflammatory conditions: a peak falling within 48 hours of the initial toxic stimulus with a half-life of 20-36 hours.**

- **Patient having a primary or secondary peak suggests secondary infection.**
- **A PCT of <0.2ng/ml suggests bacterial meningitis is very unlikely.**
- Most patients with bacterial meningitis will have PCT levels <1ng/ml.
- **With successful antibiotic therapy, PCT levels should fall with a half-life to 20-36 hours.**

**Cautions**

- **Patients that may cause increased values without bacterial infection include:**
  - Small trauma, surgery or malignant C-cell carcinoma of the thyroid.
  - Early studies including major trauma, major surgical interventions or severe burns.
  - Prolonged severe organ hypertension or cardiacogenic shock.
  - Newborns in the first few days of life.

- **After removal of the noxious stimulus, PCT should start to fall.**
- **Patients with untreated end-stage renal failure may have levels of 5-20ng/ml due to the potential of infection or severe inflammation. Within 3 hours, PCT should fall to within the normal reference range.**
- **End-stage renal failure patients on dialysis have PCT levels that are elevated in non bacterial infections.**
- **If the exacerbation of a chronic inflammatory disease is a low but definite possibility of false-positive results in patients with underlying chronic inflammatory disease.**
- **If the clinical picture should therefore be discussed with the laboratory.**

**C-REACTIVE PROTEIN (CRP)**

CRP is an acute phase reactant protein produced by the liver in response to interleukin-6 produced during inflammation of any type. It is the most sensitive of acute phase reactants, the concentration increases rapidly during inflammation. It was first described in 1930 following its observed reaction with the cell wall component of Streptococcus pneumoniae. Other than binding to cell wall of bacteria it also binds to other proteins such as chromatin and nuclear proteins. It plays a role in the innate immune response by activating the classical complement pathway. It also activates the phagocytic cells, a role in attherosclerosis and mediates tissue damage during cardiovascular disease.

The CRP-response frequency precedes clinical symptoms indicating an inflamatory increase within 6 hours of a stimulus and peaks within 24-36 hours. It’s response may be less pronounced in those with liver disease.

**Normal levels are usually below 5mg/l.**

**Uses**

CRP is used mainly as a marker of inflammation. Apart from liver failure, there are known factors that may cause CRP to increase with antibiotics.

**Interpretation of results**

- **CRP is used as an acute phase reactant protein.**
- **Differential diagnosis of bacterial infection includes:**
- **Assessment of treatment of bacterial infections with antibiotics**
- **Diagnosis of renal involvement with paediatric and chronic kidney disease**

CRP is not specific to any particular cause of inflammation. It is raised as a result of inflammation irrespective of the cause. An elevated CRP level does not diagnose an infection.

In elevated CRP level can provide support for the presence of an inflammatory process.

**Conclusion**

- **CRP is a useful marker of systemic inflammation.**
- **It has no place in the early identification of infection, but can provide useful information in the diagnosis of inflammatory processes.**

**Key to diagnostic excellence**

**References**

1. **Mooreky Y: Procalcitonin, C-reactive protein and procalcitonin/sepsis.** Clin Microbiol Infect 2005;11:8167-8171
4. **Sander T, Schettl M, Schenker S, Schleppe H: Differential diagnosis of bacterial infection and C-reactive protein response in kidney disease using**
≥100ng/mL at 24 hours and ≥50ng/mL at 48 hours of age. Adult levels should apply at ≥72 hours. Diagnosis of renal involvement in paediatric urinary tract infections: In children with urinary tract infections, a PCT level of >0.5ng/mL has a 70%-90% sensitivity and 80%-90% specificity for renal involvement. PCT levels in neutropaenic patients with infection are still significantly elevated, although induction may be reduced. A lower limit value of 0.25ng/mL increases diagnostic reliability in this group. In the appropriate clinical setting, a PCT of >2.0ng/mL predicts sepsis and a level of >10ng/mL suggests septic shock. Reported sensitivity and specificity for the diagnosis of sepsis range from 60%-100%, depending on underlying and coexisting diseases and the patient populations studied. The higher the PCT level the worse the prognosis. PCT concentrations of >20ng/mL are associated with a guarded prognosis. When sepsis has been successfully treated, PCT levels should fall with a half-life of 20-36 hours.

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