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Review Article

Procalcitonin: In diagnosis of paediatric infections

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ABSTRACT

Although there are many diagnostic tests available for the diagnosis of infections, all have their own limitations with regard to time, sensitivity and specificity. As a result, there is an unnecessary and prolonged use of antibiotics, leading to multidrug resistance and antibiotic misuse. Increasing evidence supports the use of procalcitonin (PCT) in diagnosing bacterial infections as early as possible and titrating the antibiotics according to the dynamics of PCT value. PCT helps in the early diagnosis of the upper and lower respiratory tract infections, meningitis, post-operative cases, sepsis in intensive care units and the judicial use of antibiotics according to PCT algorithms. PCT is a reliable marker as compared to the other markers such as C-reactive protein, interleukin 1, 6, IF-gamma and tumour necrosis factor-alfa. PCT value is not affected by neutropenia, immunodeficiency disorders and with the use of steroid and non-steroid anti-inflammatory drugs. The aim of this review article is to summarise the current evidence for PCT in different infections and clinical settings and discusses the diagnostic and prognostic value of PCT in different types of infections, its limitations and the economics of usage of PCT.

Keywords: Procalcitonin, C-reactive protein, Bacterial infection

INTRODUCTION

In treating paediatric patients, accurate diagnosis of bacterial infection is important for timely starting antibiotics and child management.[1,2] Today, many diagnostic markers are available but still diagnosing bacterial infection in a short time period is quite challenging. Blood culture is a gold standard despite the fact that it takes at least 48 h with a sensitivity of 60–70% only.[3] Inflammatory markers, such as C-reactive protein (CRP) and total leucocyte count (TLC), are lacking in specificity for the diagnosis of bacterial infections. This is because of the complex interactions of different pro- and anti-inflammatory mediators between the host and the invading pathogens with the emergence of antibiotic resistance; we need to be more careful while using antibiotics empirically. Inflammatory markers, which are mainly used like TLC and CRP, have low specificity for diagnosing bacterial infections.[4]

As potentially a more specific marker for bacterial infection, procalcitonin (PCT) has triggered greater interest. PCT is produced ubiquitously in response to endotoxin or mediators released in response to bacterial infections (i.e., interleukin [IL]-1β, tumour necrosis factor [TNF]-α and IL-6) and strongly correlates with the extent and severity of bacterial infections.[5,6] Endotoxin or mediators which are produced in response to bacterial infections, that is, IL-1β, IL-6 and TNF-α stimulate the production of PCT, which effectively correlates with the severity of the disease caused by bacterial infections.

WHAT IS PCT?

PCT is the peptide precursor of calcitonin, which is composed of 116 amino acids. It is synthesised by the parafollicular C cells of the thyroid and some amount from neuroendocrine cells of the lungs and small intestine. Endopeptidase-cleaved pre-procalcitonin gives rise to PCT. PCT level is attenuated by post-viral infection-induced cytokine release, interferon-g, so PCT is more specific for bacterial infections and helps to distinguish between bacterial and viral infections. PCT shows a promising kinetic profile for use as a clinical marker as within 6–12 h of stimulation it starts and the circulating levels will be reduced to half daily when the infection is controlled either by antibiotic use or because of the host immune system.[7]

The serum concentration of PCT in a normal individual is either non-detectable or <0.05 ng/ml, when there is systemic inflammation, particularly because of bacterial infection PCT level will increase drastically up to 1000 times.[8,9] This is because of endotoxin produced by bacteria or because of the inflammatory mediators released due to underlying bacterial infection. PCT is produced in a number of tissues such as the lung, liver, kidney and adipose tissue. In contrast to CRP level which takes 12–24 h to reach the maximum level after bacterial infection, PCT level starts rising soon after 2–4 h of infection and reached the maximum level in 6–24 h. Another advantage of PCT over CRP is that PCT serum level is not affected by immune deficient conditions, case of neutropenia or cases where steroids or other nonsteroid anti-inflammatory drugs used.[10]

PCT level is associated with the severity of infection and intensity of inflammation. Hence, it is associated with a severe form of the disease and poor prognostic factor. Depending on the method used, the level of PCT in the patient's blood can be determined in a range from 19 min to 2.5 h.[11]

It has been shown that the inclusion of PCT in therapeutic guidelines reduces the use of antibiotics, with no negative effects on the final outcome of the disease, both in inpatient and outpatient practice.[12,13] PCT has good diagnostic and therapeutic significance but it should be used in combination with other significant laboratory makers and clinical observation.[14]

PRINCIPLE AND PROCEDURE

The one-step immunoassay sandwich method with a final fluorescent detection enzyme-linked fluorescence assay incorporates the assay principle.

PROCEDURE

A solid phase receptacle (SPR) which serves as a solid phase besides pipetting device helps in the estimation of PCT. This interior of the SPR is coated during production with mouse monoclonal anti-PCT immunoglobulins. The other one is the reagent strip which consists of 10 wells covered with a labelled and foil seal. The human serum or plasma (lithium heparin) of 200 µL sample is required to perform the test and the test takes 1 h time for the entire procedure.

DIAGNOSTIC VALUE OF PCT

The most important thing about adding PCT in therapeutic applications is that it decreases the over and prolonged use of antibiotics without any adverse effect on the final outcome of the disease. Some of the indications where PCT is useful are:

- For the diagnosis and risk stratification of bacterial infection[15,16]
- To diagnose urinary tract infection in children with renal involvement
- To differentiate bacterial versus viral infection, including meningitis[17]
- To decrease antibiotic exposure and monitor the therapeutic response to antibiotic therapy
- In case of surgery and severe trauma or burns and multiorgan failure case PCT level helps in the diagnosis of secondary infection[18]
- In acute pancreatitis helps in the diagnosis of systemic complications.

SOME OF THE PROPOSED APPLICATIONS ARE

- It is used for assisting the prognosis of severe localised infections such as pneumonia[19]
- In critically ill patients with systemic infection helps in explaining the prognosis
- As well as in starting antibiotics in case of elevated PCT, its normal level can guide us to discontinuing antibiotics, this will reduce antibiotic use and help in antimicrobial stewardship.[20]

PROGNOSTIC VALUE OF PCT

- Persistently, high PCT level is an indicator of ongoing inflammation and suggestive of poor prognosis
- Declining values suggest a good prognosis, it indicates the removal of infection and decline in inflammatory reaction
- Dynamics help to titrate the antibiotics with the best outcome.

REFERENCE VALUES AND INTERPRETATION

Reference values of PCT in adults and children are <0.05 ng/mL. Mildly raised pct (0.05 to 2 ng/ml) can be seen in localized bacterial infection, non infectious inflammatory conditions and end stage renal failure.

In case of bacterial sepsis or severe localised bacterial infection (such as severe pneumonia, meningitis or peritonitis), severe non-infectious inflammatory stimuli (such as a major burn, severe trauma, acute multi-organ failure or major abdomen or thoracic surgery) or medullary thyroid carcinoma, PCT levels are significantly raised more than 2 ng/ml.

In the case of a normal full-term newborn, PCT level starts increasing after birth gradually and reached its peak level within 24 h of life. After that, it starts reducing and again come to a normal value of <0.05 ng/ml by 48–72 h of life. Many studies done in children and neonates have demonstrated that >after 72 h of age, PCT values <0.5 ng/ml are considered to be normal; any increase in PCT level to 0.5–2 ng/ml is because of due to non-infectious inflammation conditions, or either viral or focal bacterial infections; PCT level 2–2.5 ng/ml after 72 h of life, suggests either a bacterial infection or systemic fungal infection. In meta-analysis done by Pontrelli *et al*. in 2017 also supports similar findings and shows that to diagnose sepsis in newborns, the cutoff of value of PCT 2–2.5 ng/ml has moderate accuracy and best sensitivity.[21] Stocker *et al*. also find in their study that after 72 h, PCT-guided antibiotic therapy has significantly reduced antibiotic use and reduced antibiotic therapy to 22.4 h.[22]

KEY PRINCIPLES OF PCT INTERPRETATION

1. Interpretation of PCT should always be considered in the clinical context of the patient, for instance in patients with septic shock with normal PCT, antibiotics should not be withheld
2. Serial measurement of PCT level gives better clue than a single measurement. In case of bacterial infection, early measurement of PCT will be negative but subsequent value shows an increasing trend. Patients whose PCT value is persistently negative are less likely to have a systemic bacterial infection. Patients who have steadily decreasing PCT levels after major surgery often do not need antibiotics
3. Dynamics of the disease need to be considered, PCT levels steadily decline in patients with severe trauma without infection and severe infection such as bacterial pneumonia will take a longer time for PCT to come down
4. In COVID infection: Significantly elevated PCT is usually associated with a high risk of developing severe SARS-CoV2 infection. Despite the fact that many patients with mild to mederate COVID infection, will have normal PCT levels. PCT levels are significantly elevated in bacterial infection and serial PCT measurement may play a role in predicting disease progression.[23]

LIMITATIONS OF PCT

The clinical scenario should always be considered while interpreting PCT results since there is a chance of either being a false positive or false negative.

Non-bacterial causes of raised PCT level:

- Newborn in the early neonatal period (<72 h of life)
- Sever stressful conditions such as severe trauma, surgery, cardiac shock and severe burns[24-26]
- Medication that stimulates cytokines – OKT3, anti-lymphocyte globulins, granulocyte transfusion, IL-2 and alemtuzumab
- Some fungal infections and malaria
- Case where organ perfusion is compromised like prolong cardiogenic shock, some vasculitis and acute graft versus host reaction
- Medullary thyroid-induced paraneoplastic syndrome
- Renal failure cases especially those who have end-stage renal disease and on haemodialysis.

Different pathogens have a distinct response in inducing the circulatory level of PCT[27]

- In case of atypical pneumonia-like mycoplasma will not lead to raise high PCT level as it causes in case of pneumonia caused by pneumococcal infection[28]
- High PCT did not consistently indicate bacterial coinfection in critical viral illnesses.[3]

The previous antibiotic therapy can lead to a low PCT value; similarly, if the bacterial load is low in that case also PCT might persistently be on the lower side.

- Low PCT indicates that CNS infections are unlikely[3]
- In suspected patients of pneumonia who present with complaints of dyspnoea, the accuracy of PCT is moderate and lower than that of (IL)-1β-6 and CRP.[29]

COSTS

Although PCT test cost is high and almost double that of CRP, it provides better clinical benefits in managing patients. In the end, preventing excessive antibiotic use and stopping it early, it will ultimately reduce the overall cost of patient management. It will also reduce antibiotic-related adverse drug reactions and reduce hospital stays.

THE USEFULNESS OF PCT OVER CRP

PCT is very early detected in the blood than CRP and is not affected by use of non-steroidal and steroid anti-inflammatory drugs. It is a more useful diagnostic parameter than CRP in patients with paediatric neutropenic fever. PCT value starts raising soon within 4 h of the onset of systemic infection, it reaches peak value in 6–8 h and remains high for at least 24 h.[22] The increase in peak values of PCT is observed more rapidly before the CRP, PCT rises in a shorter

time frame and serves as a monitoring biomarker since its levels return to normal much faster than those of CRP when the patient responds appropriately.[30,31]

PCT VERSUS CRP

To evaluate the efficacy of PCT and CRP levels for the diagnosis of bacterial infection, meta-analysis was performed which showed sensitivity for PCT was higher (92% [95% CI, 86–95%] versus 86% [95% CI, 65–95%]); PCT had higher diagnostic accuracy for patients admitted for suspected bacterial infection.[32]

There are multiple studies available that suggest PCT is more valuable in distinguishing bacterial infection, it is more accurate to differentiate sepsis from systemic inflammatory response syndrome (SIRS).[33-37]

CONCLUSION

PCT is a reliable marker that contributes to the early diagnosis of invasive bacterial infection in children and neonates both in intensive care unit and outpatient department practice. A sequenced way of measuring of the PCT and the dynamics helps to titrate the antibiotics and prevent overuse of antibiotics. It is useful in the case of early diagnosis and treatment of sepsis, meningitis and urinary tract infections. The cost of the treatment can also be reduced by proper diagnostic and therapeutic protocols and also multidrug-resistant strains of bacteria. PCT has proven higher sensitivity (85%) and specificity (91%) to differentiate SIRS from those with sepsis, which is better as compared to other inflammatory markers such as CRP, IL-6, IL-2, IL-8 and TNF-alpha.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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