Role of Procalcitonin as a Diagnostic Biomarker of Bacterial Sepsis and a Guide to Decide Antibiotic Therapy

Ramesh Pradhan, Yagnya Dalal** , Yash Patel****

Abstract :

There are many limitations in using traditional diagnostic markers such as C-reactive protein (CRP), LDH, WBC count, ESR, clinical features in diagnosing the etiology of severe systemic inflammation and deciding antimicrobial treatment in patients with infectious ailments. As a result, there may be unnecessary and prolonged usage of antibiotics. This may be responsible for rise in antibiotic resistance and adverse patient outcome. Evidences support the role of procalcitonin (PCT) to improve the diagnosis of bacterial infection and serial PCT estimation in guiding appropriate antibiotic therapy. The aim of this review is to summarize the role of PCT in bacterial infection and discuss its reliability in ascertaining antibiotic therapy.

Key Words : Antibiotic therapy, Biomarker, Procalcitonin, Sepsis

Introduction :

Life threatening organ dysfunction in critically ill patients is either due to or accompanied with deregulated immune response; the etiology being infectious or noninfectious.[1] Similarities of presentation of both types of responses make the diagnosis difficult.[1] There are many noninfectious conditions where specific biomarkers have been implemented. They are Troponin I in acute myocardial infarction, D-Dimer in pulmonary embolism, Natriuretic peptides in acute cardiac failure. Still a timely diagnosis of bacterial infection is a challenge.[2] Reliable clinical and/or microbiological parameters from easy to obtain specimens that may be used to diagnose bacterial sepsis and rule out other infections not requiring antibiotic therapy are largely lacking. Many current diagnostic procedures for bacterial infection lack promptness (e.g., culture methods), sensitivity (e.g., blood culture) and specificity (e.g., sputum culture).[2] There are more than 200 inflammatory biomarkers potentially available for diagnosis of infectious illnesses, but PCT and CRP are most commonly used.[1] CRP lacks specificity for bacterial infections. It has long half life and a slow response – it reaches the maximum concentration in 48 hours after insult.[3] So CRP levels may mislead or delay the diagnosis of bacterial infection and hence its appropriate treatment. Early diagnosis of infection is of physiological and clinical importance. Earlier identification of infection expedites timely measures to overcome it.[3] In such diagnostic dilemma, PCT has emerged as a more specific marker for bacterial infection. Bacterial endotoxins or exotoxins set in the cascade of inflammation, which in turn releases the mediators (IL-1, TNF-, IL-6). PCT is produced in response to these mediators. PCT is markedly raised within 2 – 4 hours of infection and the level persists until recovery.[4] Biological half life of PCT is 22 -26 hours.[5] Interferon^{+}; a cytokine released due to viral infection attenuates the up regulation of PCT by inhibiting TNF synthesis. So PCT is not raised in viral illnesses.[2] Thus PCT may help to distinguish bacterial infection from viral illnesses.[6] Circulating PCT levels halve daily when infection is controlled by immune system of body or antibiotic therapy.[7] PCT levels are directly proportional to bacterial load and severity of infection.[8, 9] Thus, PCT is a reliable prognostic marker in predicting outcome of sepsis patients.[10] There are other biological roles for PCT beyond aiding in diagnosis of bacterial infection, which require further study. [4]

Biochemistry of PCT [11]:

PCT is a 116 amino acid peptide with approximate molecular weight of 14.5 kDa. It belongs to Calcitonin (CT) superfamily of peptides. PCT is encoded by CALC-1 gene located on chromosome-11. Cleavage of CALC-1 gene produces preprocalcitonin which further

** Undergraduate Medical student, GCS Medical College, A'bad
*** Ex-Intern Doctor, GCS Medical College, Hospital & Research Centre, Ahmedabad, Gujarat, India
* Professor & Head, Dept. of Biochemistry, GCS Medical College, Hospital & Research Centre, Ahmedabad, Gujarat, India
Correspondence : Dr. Ramesh Pradhan
E-mail : romu11@rediffmail.com

undergoes proteolytic cleavage into PCT. In absence of infection, transcription of CALC-1 gene is suppressed except in parafollicular cells of thyroid gland. In parafollicular cells, PCT is produced which is processed to Calcitonin and then it is stored into secretary granules. In presence of bacterial infection, there is substantial increase in expression of CALC-1 gene in all paranchymal tissues and thus substantial increase in PCT levels.

Measurement of PCT:

Currently all methods for PCT estimation are based on immunoassay techniques on serum, heparinised plasma or K+ EDTA plasma. Reference interval in healthy individuals (adults) is ≤ 0.05 ng/mL. Samples should preferably be processed and analysed within four hours of blood draw or otherwise should be stored at 2-8 °C for up to 24 h, and frozen at -20 °C if estimation is to done within 48 h. A single freeze-thaw cycle may lead to a reduction in recovery of up to 8%.

Samples need centrifugation prior to analysis to ensure they are free of fibrin or other particulate matter as fibrin may show false low values. Limitations could be higher values as a result of pro-inflammatory stimuli such as surgical trauma also.

Observations [2] :

From different Observational and Randomized controlled intervention studies; available evidence on role of PCT has been derived as under:

(Abbreviations : + : Moderate evidence in favour of PCT, ++ : Good evidence in favour of PCT, +++ : Strong evidence in favour of PCT, # : Evidence in favour/against use of PCT still undefined)

Uses of PCT :

At present PCT levels have four common implications.[3]

(A) Correlation of PCT level with severity of infection:

PCT has proved itself superior to commonly obtain clinical parameters and other laboratory tests in diagnosis of sepsis. It has established its correlation with the extent and severity of infection. It has reliable prognostic implications, as the trend of serial PCT levels predicts the risk of mortality in critically ill patients with bacterial sepsis.[12] Unlike CRP, production of PCT is not significantly decreased by steroids or non steroidal anti-inflammatory drugs. [13]

(A) For Diagnosis Of Infection (Observational studies) :	
Bacteremia	+ +
Blood stream infections	+ +
Pyelonephritis and urinary tract infection	+ +
Endocarditis	+
Arthritis	+
Postoperative fever	+
Neutropenia	+
Pancreatitis	#
Abdominal infections	#

(B) For Antibiotic Decision (Intervention studies) :	
Upper respiratory tract infection	+ + +
Pneumonia	+ + +
COPD exacerbation	+ + +
Acute bronchitis	+ + +
Septic shock	+ + +
Ventilator associated pneumonia	+ +
Postoperative infections	+ +
Meningitis	+

(B) PCT as a guide for antibiotic treatment in Respiratory tract infections:

PCT is useful to guide the antibiotic treatment in patients of pneumonia and other lower respiratory tract infections as a surrogate biomarker. [14] Low PCT levels over first 4 hours of hospitalization have excellent negative predictive role for bacterial infection. [15] PCT levels should be rechecked after 48–72 hours of starting the antibiotic treatment for decision of discontinuation or broadening the antibiotic therapy. [16]

(C) PCT as a guide for antibiotic treatment in other infections:

PCT is proposed to be a reliable biomarker in distinguishing bacterial infections from other types of infection like neutropenic fever, fungal infections, arthritis, post-operative fever, suspected bloodstream infections.[17] Except for respiratory tract infections, meningitis, urosepsis and sepsis within ICU, no intervention studies could be found that establishes the role of PCT as a safe guide to antibiotic therapy. [18,19]

For some conditions, PCT is not sensitive enough for routine clinical use. Examples are [3] –

{a} Subacute endocarditis – PCT levels may remain low and it cannot be used to discriminate infected from uninfected patients.

{b} Mycoplasma pneumonia – PCT levels may remain low.

{c} Hypothermia after cardiac arrest – PCT levels rise initially irrespective of presence of infection.

These observations limit the potential of PCT as a guide to antibiotic therapy in such high risk patients. [3]

(D) PCT algorithms for guiding antibiotic usage:

Antibiotic resistance is a major factor affecting patient outcomes. Efforts to reduce injudicious usage of antibiotics are of paramount importance.[12] For PCT to guide the antibiotic therapy in patients with respiratory tract infection and ICU sepsis, universally accepted algorithms are followed. These algorithms recommend for and against antibiotic treatment based on PCT cut-off ranges.[2,3]

For recommendation of antibiotic discouragement, blood samples for measuring circulating PCT should be taken at the early stage and second concentration to be obtained 6-12 hours later. [20]

Guidelines for starting antibiotics [20]

PCT cut-off value (µg/L)	Antibiotic recommendation
< 0.25	Strongly discouraged
≥ 0.25 to <0.5	Discouraged
≥ 0.5 to <1	Encouraged
≥ 1	Strongly encouraged

Limitations and uncertainties:

Sepsis is a consequence of different infectious etiologies and is too complex to be reduced to a single cut-off of any biomarker. So PCT measurements may be limited by false positive and false negative results.[6] Different pathogens induce different responses with resultant variable up-regulation of circulating PCT levels.[22] There are certain conditions where PCT elevation occurs in absence of infection. [3] They are –

Major trauma, postoperative states, burns, cardiac shock, medullary thyroid cancer, small cell cancers of lung, carcinoid syndrome, pancreatitis, pulmonary inhalation injuries, heat stroke, mesenteric infarction, birth stress in newborn, graft-versus-host-disease, Kawasaki disease etc. Certain therapies can also cause rise in serum PCT levels – e.g., granulocyte transfusion,

Guidelines for continuing or stopping of antibiotics [20]

PCT cut-off value (µg/L)	Antibiotic recommendations
<0.25	Stopping strongly encouraged
Decrease by ≥ 80% from peak concentration, or concentration >0.25 and <0.5	Stopping encouraged
Decrease by <80% from peak concentration and concentration >0.5	Continuation encouraged
Increase of concentration compared with peak concentration and concentration >0.5	Changing of antibiotic strongly encouraged

Interpretation of PCT concentration: (Adapted from Meisner M.) [21]

PCT (g/L)	Interpretation
<0.05	Healthy adult
0.05 - <0.5	Systemic infection is unlikely although localized infection is possible
0.5 - <2	Systemic infection is possible but other conditions (eg. major trauma, recent surgery, severe cardiogenic shock) may also induce significant PCT rise
2 - <10	Systemic infection is likely
≥ 10	High likelihood of severe bacterial sepsis or septic shock

administration of antilymphocyte globulin or anti-CD3 antibodies, therapy with cytokines or related antibodies (IL-2 or TNF). [20]

Summary and conclusion:

Role of PCT in diagnosing bacterial origin of systemic inflammation has gained widespread support. Although PCT has proved itself to be an interesting marker of sepsis, its physiological role is unclear.[11] Almost lack of PCT expression in healthy state and its expression in almost every organ during sepsis leads to a belief that it is associated with "Organ Shutdown" of severe sepsis. [11] This marker would help in early diagnosis of bacterial sepsis and differentiation of infectious from noninfectious causes of systemic inflammation. Serial estimation of PCT is of great value as a prognostic predictor of severe sepsis and also helps managing antibiotic therapy. Further research aimed at explaining the role of PCT would widen the road of understanding the pathogenesis of sepsis and help develop more effective therapeutic regimens.

Abbreviations:

CRP: C-reactive protein

LDH: Lactate dehydrogenase

WBC: White blood cells

ESR: Erythrocyte sedimentation rate

PCT: Procalcitonin

CT: Calcitonin

TNF: Tumor necrosis factor

IL: Interleukin

ICU: Intensive care unit

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