International Journal of Advanced Science and Technology
Vol. 29, No. 12s, (2020), pp. 520-528

Serum Procalcitonin (Pct) As A Promising Marker For Making Diagnostic And Antibiotic Stewardship In Different Bacterial Infections

Dr. Santhoshini Vaijinath[1], Dr. Sangeetha S[2]
[1]*Assistant Professor, Department of Microbiology*
[2]*Professor, Department of Microbiology*

Abstract

Procalcitonin (PCT), a protein that consists of 116 amino acids, is the peptide precursor of calcitonin, The final step in the synthesis of calcitonin is inhibited by cytokines and endotoxin released during bacterial infections; therefore, procalcitonin levels are selectively elevated in patients with bacterial infections. Because of the diverse etiologies of community-acquired pneumonia (CAP) and the limitations of current diagnostic modalities, serum procalcitonin levels have been proposed as a novel tool to guide antibiotic therapy. The clinical utility of serum procalcitonin (PCT) levels continues to manifest. Procalcitonin (PCT), has recently become of interest as a possible marker of the systemic inflammatory response to infection. Numerous studies abroad have proved its efficacy as a marker of critical illness. Fortunately no similar studies exist in Indian literature.The aim of this review is to summarize the current evidence for PCT in different bacterial infections and clinical settings, and to discuss the reliability of this marker when used with validated diagnostic algorithms.

Keywords: *Antibiotic; Bacterial infections; Biomarker; Procalcitonin; Stewardship.*

INTRODUCTION

During the course of evolution, our immune system has eventually developed to deal with infectious pathogen invasions by various host defence mechanisms. Inflammatory response is one of the primary responses to a microbial invasion, which leads to the systemic illness which is referred to as sepsis. Its severity correlates with mortality [1]. It may occur as a result of infections acquired from community, hospitals or other healthcare facilities. There is an alarming number of 18 million new sepsis cases reported each year worldwide with mortality rate ranging from 30–50% . Intensive care case pattern study reported frequent prevalence of sepsis in India, with 28.3% of patients contact sepsis during ICU stay and have 34% mortality rate [2].The isolation of causes is considered as the golden standard of diagnosing bacterial infections and sepsis. However, due to the time required for the implementation and interpretation of the results of blood and other bacterial cultures, insufficient sensitivity (blood culture) and low specificity caused by contamination (sputum), under the modern understanding of the definition, identification of bacterial pathogen today does not present the condition that determines the diagnosis of sepsis [3]. About 70% of radiologically proven pneumonia and up to 80% of clinically suspected bacteremia remain microbiologically undifferentiated [4]. In medical practice there is an emphasized tendency of doctors– clinicians to define reliable diagnostic parameters that would allow quick confirmation of bacterial infections in the early stage, when the disease manifests itself only as a vague fever, with no other general or local symptoms [5]. The results of researches, which in recent years have been focused on the acute phase reactants of inflammation, indicate considerable diagnostic potential of procalcitonin (PCT) in the early detection of bacterial infection and its correlation with disease severity and outcome of treatment [6]. A growing body of evidence supports the use of PCT as a marker to improve the diagnosis of bacterial infections and to guide antibiotic therapy[7]. Over the past 15 years, the use of PCT in identifying the bacterial or non-bacterial origin of systemic inflammation has been gaining widespread support, and it is likely this trend will continue.

OVERVIEW OF SEPSIS

Sepsis refers to the systemic response to infection by microbial agents, such as bacteria, fungi, and yeast, where the patient typically develops fever, tachycardia, tachypnea, and leukocytosis. Microbiologic cultures from the blood or the infection site are frequently, although not invariably, positive [8]. Severe sepsis is associated with the hypoperfusion or dysfunction of at least 1 organ. When severe sepsis is accompanied by hypotension or multiple organ system failure, the condition is known as septic shock. Epidemiological studies indicate an incidence of approximately 750,000 sepsis cases per year in the United States [9]. The signs and symptoms of sepsis are highly variable and are influenced by many factors, including the virulence and bioburden of the pathogen, the portal of entry, and the host susceptibility. Primary sites are respiratory tract infections, followed by genitourinary infections, and gastrointestinal infections. Recently there has been an increasing number of reports on bacterial infections of hospitalized patients due to increased nosocomial infections from catheterization and immunosuppressive therapies, in addition to increased causes of methicillin-resistant Staphylococcus aureus (MRSA). Distinguishing inflammation due to bacterial, other microbial infection, or organ rejection is important in the treatment of the immune reaction in hospitalized patients[10]. A common problem in the clinical practice is that the signs and symptoms of bacterial and viral infections are widely overlapping, especially in respiratory tract infections. Occasionally the diagnostic uncertainty still remains, even after obtaining a patient history, performing a physical examination, chest x-ray test, and laboratory tests. Thus, a laboratory test with more specificity would significantly improve the clinical differential diagnosis in these cases. In addition, the differential diagnosis of infection would help in deciding whether treatment with antibiotics would be beneficial. In this regard, approximately 75% of all antibiotic doses are prescribed for acute respiratory infections that have a predominantly viral etiology.5 The excessive use of antibiotics is the main cause for the spread of antibiotic-resistant bacteria. Thus, decreasing the use of antibiotics is essential in combating the increase of antibiotic-resistant micro-organisms[11].

PROCALCITONIN (PCT)

Each hormone in the body has a precursor from which it is formed. In the case of calcitonin, a hormone produced by the thyroid gland, its peptide precursor is represented by *procalcitonin*. The main role of calcitonin as a hormone in the body is to maintain the homeostasis of the calcium metabolism [12]. Procalcitonin, composing of 116 amino acids, is a peptide precursor of the hormone calcitonin. It is produced by the parafollicular cells of the thyroid and neuroendocrine cells of the lungs and intestines [13]. Procalcitonin has been found in many studies to be elevated in patients with sepsis and severe infections, while remaining at normal levels with noninfectious stimuli, with concentrations closely associated with the severity of the bacterial infection [14].

In today's clinical practice, procalcitonin (PCT) has developed into a promising new biomarker for early detection of (systemic) bacterial infections. PCT is a 116-amino acid residue that was first explained by Le Moullec et al. in 1984; however, its diagnostic significance was not recognized until 1993[15]. In 1993, Assicot et al. demonstrated a positive correlation between high serum levels of PCT and patients with positive findings for bacterial infection and sepsis (eg, positive blood cultures). Further, they demonstrated that PCT did not elevate in viral infections and that serum levels of PCT would decrease following administration of appropriate antibiotic therapies [16]. Current inflammatory biomarkers, such as C-reactive protein (CRP), lack the specificity required to diagnose bacterial versus non-bacterial infections accurately[17]. Therefore, PCT assays with a specificity of 79%, have since been developed and utilized to more accurately determine if a bacterial species is the cause of a patient's systemic inflammatory reaction[18].

Healthy patients have procalcitonin levels below 0.1 ng/ml, while patients with severe bacterial infections have levels above 0.5 ng/ml[19]. It is however, less useful as a prognostic marker for outcome following infections[20]. Serum procalcitonin has also been found to be a useful marker in differentiating bacterial

and viral meningitis with good sensitivities and specificities. However, differentiating ventriculitis and bacterial meningitis in Intensive Care Unit patients with shunts and ventriculoperitoneal shunt infections have been less promising[21]. Studies have also shown that there is a strong link between poor neurological outcome and high serum procalcitonin levels in postcardiac arrest patients [22].This was postulated to be the result of an acute phase response to hypoxia as these levels were taken from patients who did not exhibit features of systemic inflammatory response syndrome or sepsis.

PATHOPHYSIOLOGY

Under normal homeostasis, pre-procalcitonin undergoes initial synthesis by thyroid C cells. Later this peptide is transformed into procalcitonin via cleavage of a 25-amino acid signal sequence by endopeptidases. The end product calcitonin, the 32-amino acid hormone responsible for serum calcium regulation, is then formed following conversion by the enzyme prohormone convertase[23]. Normally, physiological conditions result in very low serum procalcitonin levels (less than 0.05 ng/mL). However, the synthesis of PCT can be increased (up to 100 to 1000 fold) as a result of endotoxins and/or cytokines (eg, interleukin (IL)- 6, tumor necrosis factor (TNF)-alpha, and IL-1b), which act on various tissues [24]. The extra-thyroid synthesis of PCT has been found to occur in the liver, pancreas, kidney, lung, intestine and within leukocytes; however, it merits noting that the synthesis of PCT has been shown to be suppressed within these tissues in the absence of bacterial infection. In contrast, cytokines, such as interferon (INF)-gamma, which get released following viral infection, lead to down-regulation of PCT, thus highlighting another advantage of PCT assays[25].

USES OF PROCALCITONIN [26]

Sepsis diagnosis

In patients who are suffering from severe bacterial sepsis, the measurement of procalcitonin can be used for the confirmation of the diagnosis. Procalcitonin is also useful in making the differential diagnosis, between the actual sepsis state and the one from the systemic inflammatory response syndrome. By measuring the procalcitonin levels, one can decide on the correct dosage of antibiotics.

Pneumonia

Studies have shown that the measurement of procalcitonin might be useful in the administration of antibiotics in patients diagnosed with pneumonia. The measurement of procalcitonin is used to reduce the usage of antibiotics is a definite advantage; all over the world, there are a lot of people who follow treatments with antibiotics when it is not necessary. In patients who suffered from chronic obstructive pulmonary disease, the measurement of procalcitonin levels contributed to the reduction of days in the hospital from 7.1 to 4.8 days.

Bacteremia

The measurement of procalcitonin is also extremely useful for the diagnosis of bacteremia, with this hormone having an increased sensitivity to bacteria present in the body. Procalcitonin levels can be measurement in other medical conditions, including in malaria. Procalcitonin levels can also be measured in patients who are suffering from pulmonary tuberculosis and in those who undergo chemotherapy for different types of cancer. It seems that the levels of procalcitonin levels can be useful in distinguishing bacterial infections caused by mycobacterium tuberculosis and pneumocystis jirovecii. High levels of procalcitonin have also been encountered in patients who have undergone organ transplants, suffering either from organ rejection or bacterial infections.

PCT MEATUREMENT IN THR DIAGNOSIS OF BACTERIAL INFECTION

Since the mid 1990s, there has been an increasing use of PCT measurements in identifying systemic bacterial infections.3 The short half-life (25–30 hours in plasma) of PCT, coupled with its virtual absence in health and specificity for bacterial infections, gives it a clear advantage over the other markers of bacterial infection[27]. Studies have also shown that an increase in PCT levels is minimal in viral infections while levels increase rapidly after a single injection with endotoxin[28]. Furthermore, elevations

in PCT are not associated with specific bacterial strains, although in a study by Rowther and colleagues, strains from septic patients with serum PCT levels >2 ng/mL were identified and listed[29]. Recently, Jacquot and colleagues demonstrated that rapid measurement of PCT could help rule out nosocomial infection in newborns hospitalized in intensive care units[30]

In another study, de Jager and colleagues investigated the value of measuring PCT levels in the blood of patients infected with community-acquired pneumonia (CAP) caused by *Legionella pneumophila* in comparison to other conventional parameters such as CRP and WBC counts[31]. They found that initial high levels of PCT were indicative of a more severe disease, and this was reflected in a longer patient stay in the intensive care unit (ICU) and/or in-hospital death. Furthermore, persistently increased levels of PCT were always indicative of an unfavorable outcome. Thus, determination of PCT levels provided valuable information on patient prognosis that could not be determined from conventional inflammatory parameters such as CRP and WBC counts. Furthermore, the use of PCT measurements to efficiently treat patients with antibiotics has been shown to decrease patient hospital stay. Kristoffersen and colleagues reported that in those patients with chronic obstructive pulmonary disease, a single serum PCT determination at the time of admission reduced the mean length of stay from 7.1 days to 4.8 days[32].

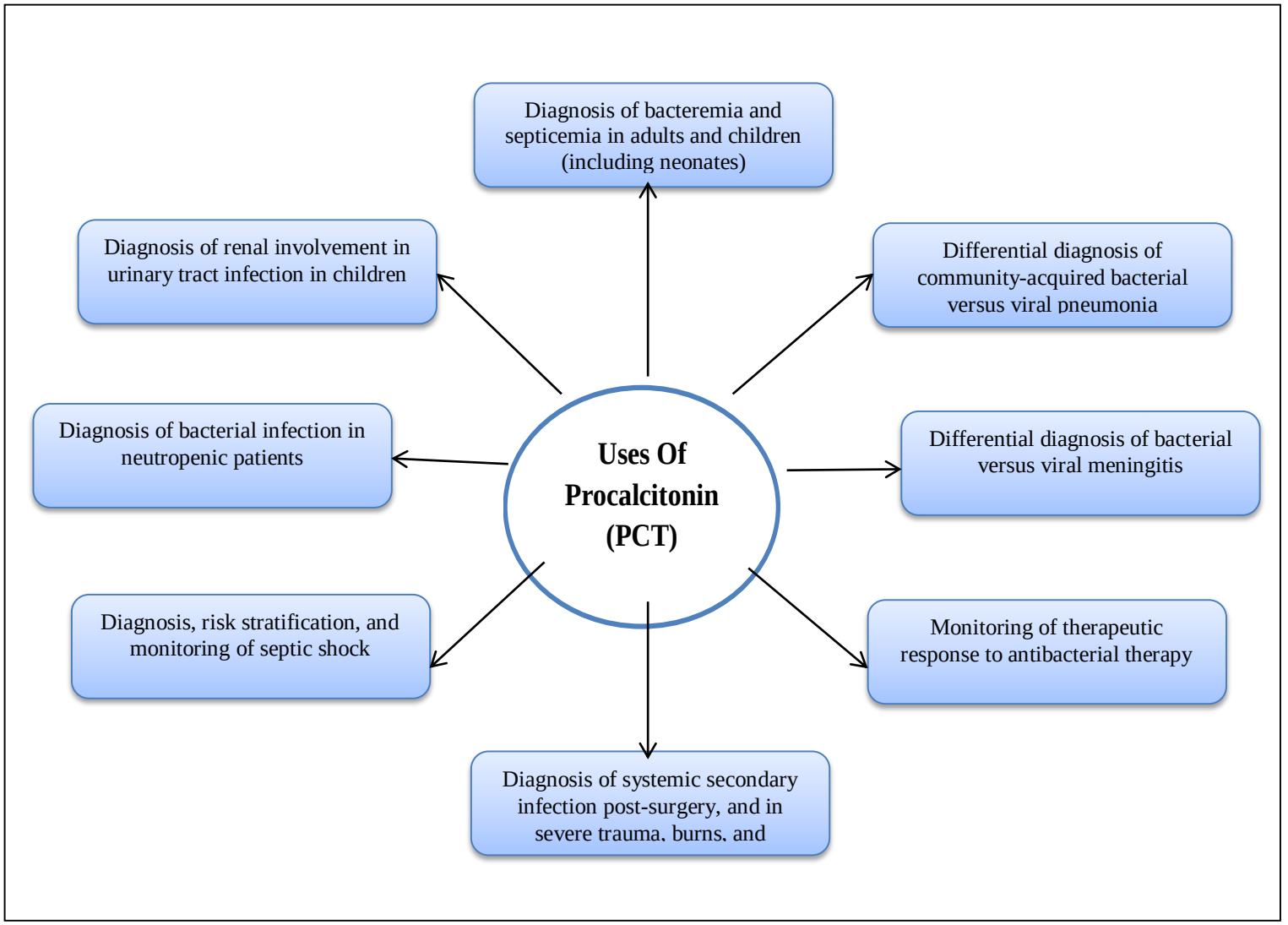

Figure 1. Schematic representation of scope of PCT in medical science

DIAGNOSTIC TEST : PROCALCITONIN

Synonym/acronym- PCT, ProCT, Sepsis PCT.

Method – Immunofluorescence immunoassay (IFA).

Commen use- To assist in diagnosing bacterial infection and risk for developing sepsis.

Specimen- Serum (2ml) collected in a gold-, red-, or red/grey-top tube. Plasma (2ml) collected in a lavender-top (EDTA) or a green-top (lithium or sodium heparin) tube is also accepltable.

Kinetics –Procalcitonin serum levels have been shown to increase 6 to 12 hours following initial bacterial infections and increase steadily 2 to 4 hours following the onset of sepsis. The half-life of PCT is between 20 to 24 hours; therefore, when a proper host immune response and antibiotic therapy are in place, PCT levels decrease accordingly by 50% over 24 hours[33].

Reference Values –

Adults and children > or =72 hours: < or =0.15 ng/mL

Children < 72 hours: <2.0 ng/mL at birth, rises to < or =20 ng/mL at 18-30 hours of age, then falls to < or =0.15 ng/mL by 72 hours of age [34].

Normal Findings [35] -

Age	Conventional Units	SI Units (Conventional Units × 1)
Newborn	Less than 2 ng/mL	Less than 2 mcg/L
18 -20 hr	Less than 20 ng/mL	Less than 20 mcg/L
48 hr	Less than 5 ng/mL	Less than 5 mcg/L
3 days – adult	Less than 0.1 ng/mL	Less than 0.1 mcg/L
Interpretive Guidelines		
Interpretation	Conventional Units	SIUnits
Bacterial infection absent or very unlikely	Less than 0.1 ng/mL	Less than 0.1 mcg/L
Bacterial infection possible; low risk for development of sepsis	Less than 0.5 ng/mL	Less than 0.5 mcg/L
Interpretive Guidelines		
Interpretation	Conventional Units	SI Units
Bacterial infection likely; development of sepsis is possible	0.5 – 2 ng/mL	0.5 – 2 mcg/L
Bacterial infection very likely; high risk for development of sepsis	2.1 – 9.9 ng/mL or greater	2.1 – 9.9 mcg/L or greater
Bacterial infection severe; septic shock is probable	10 ng/mL or greater	10 mcg/L or greater

CLINICAL INTELLIGENCE

Procalcitonin (ProCT) is a 116-amino acid precursor of calcitonin (CT). ProCT is processed to an N-terminal 57 amino acid peptide (CT [32-amino acids] and a 21-amino acid C-terminal peptide, catacalcin [CCP-1]). Expression of this group of peptides is normally limited to thyroid C cells and, to a small

extent, other neuroendocrine cells. CT is the only hormonally active of these peptides. CT is secreted by C cells in response to hypercalcemia and inhibits bone resorption by osteoclasts, minimizing oscillations in serum calcium and calcium loss.

During severe systemic inflammation, in particular related to bacterial infection, the tissue-specific control of CT-related peptides expression breaks down and ProCT and CCP-1 (referred collectively to as ProCT) are secreted in large quantities by many tissues. CT levels do not change.

Noninfectious inflammatory stimuli need to be extremely severe to result in ProCT elevations, making it a more specific marker for severe infections than most other inflammatory markers (cytokines, interleukins, and acute-phase reactants). ProCT elevations are also more sustained than those of most other markers and occur in neutropenic patients. This reduces the risk of false-negative results.

ProCT becomes detectable within 2 to 4 hours after a triggering event and peaks by 12 to 24 hours. ProCT secretion parallels closely the severity of the inflammatory insult, with higher levels associated with more severe disease and declining levels with resolution of illness. In the absence of an ongoing stimulus, ProCT is eliminated with a half-life of 24 to 35 hours, making it suitable for serial monitoring. Finally, the dependence of sustained ProCT elevations on ongoing inflammatory stimuli allows identification of secondary septic events in conditions that can result in noninfectious ProCT elevations, such as cardiac surgery, severe trauma, severe burns, and multiorgan failure. ProCT levels should fall at a predictable pace in the absence of secondary infection [36].

INTERPRETATION [37]

General considerations:

- ✓ In children older than 72 hours and in adults, levels below 0.15 ng/mL make a diagnosis of significant bacterial infection unlikely.
- ✓ Procalcitonin (ProCT) between 0.15 and 2.0 ng/mL do not exclude an infection, because localized infections (without systemic signs) may be associated with such low levels.
- ✓ Levels above 2.0 ng/mL are highly suggestive of systemic bacterial infection/sepsis or severe localized bacterial infection, such as severe pneumonia, meningitis, or peritonitis. They can also occur after severe noninfectious inflammatory stimuli such as major burns, severe trauma, acute multiorgan failure, or major abdominal or cardiothoracic surgery. In cases of noninfectious elevations, ProCT levels should begin to fall after 24 to 48 hours.
- ✓ Autoimmune diseases, chronic inflammatory processes, viral infections, and mild localized bacterial infections rarely lead to elevations of ProCT of more than 0.5 ng/mL.

Specific diagnostic applications, based on the current consensus in the literature:

- ✓ Diagnosis of bacteremia in neonates: After birth ProCT values increase from birth to reach peak values at about 24 hours of life and the decrease gradually by 48 hours of life. Therefore, during the first 72 hours of life different reference ranges will apply to newborn infants at different hours of age. ProCT levels on newborns suffering from early sepsis are significantly higher than those of noninfected newborns when reference ranges by hours of age are used.(1,2) Adult levels should apply at 72 hours or more after birth.
- ✓ Diagnosis of renal involvement in pediatric urinary tract infections: In children with urinary tract infections, a ProCT level above 0.5 ng/mL has 70% to 90% sensitivity and 80% to 90% specificity for renal involvement.
- ✓ ProCT responses in neutropenic patients are similar to patients with normal neutrophil counts and function, and the cutoffs discussed under general considerations above should be used.

In the appropriate clinical setting, ProCT levels above 2.0 ng/mL on the first day of admission to the intensive care unit (ICU) represent a high risk for progression to severe sepsis and/or septic shock. ProCT levels below 0.5 ng/mL on the first day of ICU admission represent a low risk for progression to severe sepsis and/or septic shock. Reported sensitivity and specificity for the diagnosis of sepsis range from 60% to 100%, depending on underlying and coexisting diseases and the patient populations studied. The higher

the ProCT level the worse the prognosis.A ProCT level below 0.5 ng/mL makes bacterial meningitis very unlikely. Most patients with bacterial meningitis will have ProCT levels of more than 10 times this level.With successful antibiotic therapy, ProCT levels should fall with a half-life to 24 to 35 hours[38].

CIRCUMSPECTION

Severe trauma, major burns, multiorgan failure, or major surgery can cause procalcitonin (ProCT) elevations in the absence of sepsis. After removal of the noxious stimulus, ProCT should start to decrease [39].

Patients with untreated end-stage renal failure may have ProCT levels greater than 0.15 ng/mL in the absence of infection or severe inflammation [39].

Patients with medullary thyroid carcinoma or, very rarely, islet cell tumors may have significant elevations in ProCT in the absence of sepsis. In certain cases, these levels may exceed 10,000 ng/mL.

Some infants and children may have ProCT levels from 0.15 ng/mL to 0.50 ng/mL for unknown reasons.

As with all immunometric assays, there is a low, but definite possibility of false-positive results in patients with heterophile antibodies. Test results that do not fit the clinical picture should therefore be discussed with the laboratory[40].

A hook effect can occur at ProCT concentrations above 2500 ng/mL (extremely rare), resulting in a lower measured ProCT concentration than is actually contained in the specimen. This may complicate the interpretation of serial ProCT measurements in rare patients with extremely high ProCT levels. If there is clinical suspicion of this occurring, then retesting after specimen dilution should be requested [41].

CLINICAL SIGNIFICANCE

It is well-documented that early diagnosis of a bacterial infection can lead to a decrease in mortality and morbidity among all patients. Efficient diagnosis of bacterial infections allows physicians to initiate antibiotic therapy when it is deemed appropriate, thus preventing the misuse and overuse of antibiotics. As antibiotic resistance continues to rise, it has become ever more important for clinicians to determine different algorithms and laboratory tests that help sustain current antibiotic parameters. Unfortunately, most of the first-line tests for determining infection, such as blood cultures and C-reactive protein (CRP), lack the efficiency and specificity needed to treat patients promptly. Therefore, procalcitonin serum assays have been developed to provide physicians and nurses with an earlier detection method for determining the origin of a systemic inflammatory response (eg, bacterial versus non-bacterial). Early detection, in turn, limits the development of antibacterial resistance as well as patient exposure to antibiotics when they are no longer warranted [42].

CONCLUSION

The present study demonstrates serum PCT to be among the most promising bacterial markers in critically ill patients, capable of complementing clinical signs and routine lab parameters suggestive of severe infection at the time of ICU admission. Serum PCT measurement appears to be a better predictor to distinguish patients with sepsis and patients without sepsis when compared to blood cell counts or body temperature or ESR. Thus, our data raise the possibility that the addition of serum PCT to the standard work-up of critically ill patients with suspected bacterial infection could increase diagnostic certainty and improve patient management.

As bacterial drug resistance continues to rise across the globe, it has become of ulmost importance to enhance antibiotic stewardship. Overall, procalcitonin levels provide a promising lab value for identifying bacterial infections; however, this test is limited based on the clinical setting and patient population for which it is utilized. Therefore, further research studies (eg, Randomized Clinical Trials) need to be conducted prior to implementing procalcitonin guidelines for everyday clinical practice.

Inclusion of PCT in diagnostic and therapeutic protocols of bacterial infections reduces the cost of treatment and the emergence of multi-resistant strains of bacteria.The impression is that methodologically valid studies on the possible use of PCT in surgical and gynecological infections are missing, as well as reports on the results of the application of PCT algorithm in "real life", with daily medical practice, outside the scientific coarse.

REFERENCES

1. Reinhart K, Meisner M. Biomarkers in the Critically Ill Patient: Procalcitonin. Crit Care Clin. 2011;27(2):253–263.
2. Gille J.P, Hansson E.K, Gardlund B. Clinical and laboratory variables identifying bacterial infection and bacteraemia in the emergency department. Scand J Infect Dis. 2012;44(10):745–752.
3. Schuez P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection guide to antibiotic decisinon: past, present and future. BMC Medicine. 2011;9:107-109.
4. Schuetz P, Christ C.M, Muller B. Procalcitonin and other biomarkers to improve assessments and antibiotic stewardship in infections – hope for hype? Swiss Med WKLY. 2009;139(23-24):318–326.
5. Hayashi Y, Paterson D.L. Strategies for reduction in duration of antibiotic use in hospitalized patients. Clin Infect Dis. 2011;52:1232–1240.
6. Kosanke R, Beier W, Lipecky R, Meisner M. Clinical Benefit of Procalcitonin. Tanaffos. 2008;7(1):14–18.
7. Mehanic S, Baljic R. The Importance of Serum Procalcitonin in Diagnosis and Treatment of Serious Bacterial Infections and Sepsis. Mater Sociomed. 2013;25(4): 277–281.
8. Sang Tae C, Jung-Soo S. Serum Procalcitonin as a Useful Serologic Marker for Differential Diagnosis between Acute Gouty Attack and Bacterial Infection. Yonsei Med J. 2016 Sep 1; 57(5): 1139–1144.
9. Carrigan S.D, Scott G, Tabrizian M. Toward resolving the challenges of sepsis diagnosis. Clin Chem. 2004;50:1301–1314.
10. Lever A, Mackenzie I. Sepsis: Definition, epidemiology, and diagnosis. BMJ. 2007;335:879–883.
11. Assicot M, Gendrel D, Garsin H, et al. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet. 1993;341:515–518.
12. Angus D.C, Linde-Zwible W.T, Lidicker J, et al. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303–1310.
13. Agency for Healthcare Research and Quality. Effective Health Care Program. EPC Project. Project Title: Procalcitonin for diagnosis and Management of Sepsis. Research protocol. April 2011. Last accessed on 2020 May 8. Available at: http://www.effectivehealthcare.ahrq.gov .
14. Bettencourt P, Azevedo A, Pimenta J, Friões F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation. 2004;110:2168-2174.
15. Brennan N. Last accessed on 2020 May 9. Available at: http://www.brookings.edu/~/media/research/files/reports/2009/8/21%20bpc%20qualityreport/0821_bpc_qualityreport.
16. Le Moullec J.M, Jullienne A, Chenais J, Lasmoles F, Guliana J.M, Milhaud G, Moukhtar M.S. The complete sequence of human preprocalcitonin. FEBS Lett. 1984;167(1):93-97.
17. Riedel S, Melendez J.H, An A.T, Rosenbaum J.E, Zenilman J.M. Procalcitonin as a marker for the detection of bacteremia and sepsis in the emergency department. Am. J. Clin. Pathol. 2011;135(2):182-189.
18. Salinas M, Lopez-Garrigos M, Flores E, Uris J, Leiva-Salinas C. Pilot Group of the Appropriate Utilization of Laboratory Tests (REDCONLAB) working group. Procalcitonin in the Emergency Department: A potential expensive over-request that can be modulated through institutional protocols. Am J Emerg Med. 2018;36(1):158-160.
19. Hatzistilianou M. Diagnostic and prognostic role of procalcitonin in infections. Scientific World Journal. 2010;10:1941-1946.

20. Reinhart K, Karzai W, Meisner M. Procalcitonin as a marker of the systemic inflammatory response to infection. Intensive Care Med. 2000;26:1193-2000.
21. Tomio R, Akiyama T, Shibao S, Yoshida K. Procalcitonin as an early diagnostic marker for ventriculoperitoneal shunt infections. Surg Infect (Larchmt). 2013;14: 433-436.
22. Kip M.M.A, van Oers J.A, Shajiei A, Beishuizen A, et al. Cost-effectiveness of procalcitonin testing to guide antibiotic treatment duration in critically ill patients: results from a randomised controlled multicentre trial in the Netherlands. Crit Care. 2018;22(1):293-297.
23. Lippi G, Sanchis G.F. Procalcitonin in inflammatory bowel disease: Drawbacks and opportunities. World J. Gastroenterol. 2017;23(47):8283-8290.
24. Jongwutiwes U. Procalcitonin: A New Marker for Bacterial Infection. Siriraj Med J. 2007;59(7):389–394.
25. Christ C.M, Müller B. Biomarkers in respiratory tract infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. Eur. Respir. J. 2007;30(3):556-573.
26. Jin M, Khan A.I. Procalcitonin: Uses in the Clinical Laboratory for the Diagnosis of Sepsis. Laboratory Medicine.2010;41(3):173–177.
27. Schneider H.G, Lam Q.T . Procalcitonin for the clinical laboratory: A review. Pathology. 2007;39:383–390.
28. Becker K.L, Snider R, Nylen E.S. Procalcitonin assay in systemic inflammation, infection, and sepsis: Clinical utility and limitations. Crit Care Med. 2008;36:941–952.
29. Rowther F.B, Rodrigues C.S, Deshmukh M.S et al. Prospective comparison of eubacterial PCR and measurement of procalcitonin levels with blood culture for diagnosing septicemia in intensive care unit patients. J Clin Microbiol. 2009;47:2964–2969.
30. Jacquot A, Labaune J.M, Baum T.P, Putet G, Picaud J.C. Rapid quantitative procalcitonin measurement to diagnose nosocomial infections in newborn infants. Arch Dis Child Fetal Neonatal Ed. 2009;94:F345–F348.
31. Nyamande K, Lalloo U.G. Serum procalcitonin distinguishes CAP due to bacteria, Mycobacterium tuberculosis and PJP. Int J Tuberc Lung Dis. 2006;10:510–515.
32. Kotula J.J, Moore W.S, Chopra A, Cies J.J. Association of procalcitonin value and bacterial coinfections in pediatric patients with viral lower respiratory tract infections admitted to the pediatric intensive care unit. J. Pediatr. Pharmacol. Ther. 2018;23:466–472.
33. Becker K.L, Nylen E.S, White J.C, Müller B, Snider R.H. Clinical review 167: Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. J. Clin. Endocrinol. Metab. 2004;89(4):1512-1525.
34. Chiesa C, Natale F, Pascone R, et al. C reactive protein and procalcitonin: reference intervals for preterm and term newborns during the early neonatal period. Clin Chim Acta. 2011;412(11-12):1053-1059.
35. Arora S, Singh P, Singh P.M, Trikha A. Procalcitonin levels in survivors and nonsurvivors of sepsis: systematic review and meta-analysis. Shock. 2015; 43: 212- 221.
36. Reiner M.M, Khoury W.E, Canales M.B, et al. Procalcitonin as a biomarker for predicting amputation level in lower extremity infections. The Journal of Foot and Ankle Surgery. 2017;56(3):484–491.
37. Abers M.S, Musher D.M. Procalcitonin as a marker of etiology in community-acquired pneumonia. Clin Infect Dis. 2018; 66:1639.
38. Kamat I.S, Ramachandran V, Eswaran H, Abers M.S, Musher D.M. Low procalcitonin, community acquired pneumonia, and antibiotic therapy. Lancet Infect Dis. 2018;18:496–497.
39. Balk R.A, Kadri S.S, Cao Z, Robinson S.B, Lipkin C, Bozzette S.A. Effect of procalcitonin testing on health-care utilization and costs in critically Ill patients in the United States. Chest. 2017; 151:23–33.
40. Ahn S, Kim W.Y, Kim S.H, et al. Role of procalcitonin and C-reactive protein in differentiation of mixed bacterial infection from 2009 H1N1 viral pneumonia. Influenza Other Resp Viruses. 2011;5:398–403.

41. Coburn K.M, Vevea J.L. Publication bias as a function of study characteristics. Psychol Methods. 2015;20:310–330.
42. Kim S.E. Serum Procalcitonin Is a Candidate Biomarker to Differentiate Bacteremia from Disease Flares in Patients with Inflammatory Bowel Disease. Gut Liver. 2016 Jul; 10(4): 491–492.