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ORIGINAL RESEARCH

Procalcitonin: A Revolutionary Biomarker in the Diagnosis and Management of Infections

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ABSTRACT
Procalcitonin (PCT) is a peptide precursor of calcitonin, nowadays it has emerged as akey biomarker in the detection of bacterial infections.A recent study has investigated the potential role of procalcitonin in non-infectious diseases. While its major application is in infection detection, greater PCT levels have been observed in various inflammatory conditions, including acute pancreatitis, trauma, and post-surgical inflammation.
The thyroid gland C-cells produce the majority of procalcitonin. However, during infections, particularly those caused by bacteria, different tissues and organs, create more procalcitonin. Pro-inflammatory cytokines are responsible for this increase in response to bacterial endotoxins like lipopolysaccharides (LPS). In contrast, viral infections decrease procalcitonin synthesis via interferon-gamma, making PCT a helpful tool for distinguishing between bacterial and viral infections.Procalcitonin is proteolytically cleaved to generate calcitonin; however, during infection, the cleavage is partial, and procalcitonin is released into the bloodstream. PCT levels can rise dramatically within 2-6 hours of illness initiation and peak between 12-24 hours, making it an early indicator of systemic bacterial infection.Procalcitonin is also used as a diagnostic tool, and as a prognostic marker to measure mortality risk and the efficacy of treatment interventions.
PCT levels can rise in non-infectious inflammatory disorders, leading to false positives. For example, patients who have recently undergone surgery, trauma, or significant burns may have elevated PCT levels due to systemic inflammation rather than bacterial infection. Furthermore, immunosuppressed patients, such as those receiving chemotherapy or with advanced Human Immunodeficiency Virus (HIV), may have reduced PCT responses even amid severe co-infections.More research is needed to determine how PCT can be included in the care of various non-infectious illnesses and whether it can provide prognostic information in these situations.

Keywords: Procalcitonin, Biomarkers, Sepsis, Inflammatory Response, C-reactive Protein (CRP)

INTRODUCTION

Procalcitonin (PCT) has emerged as a crucial biomarker in the diagnosis and management of bacterial infections. It serves as a tool to guide clinical decisions, particularly concerning antimicrobial therapy. The significance of procalcitonin in promoting antibiotic stewardship becomes ever more critical.[1] Procalcitonin testing can assist in differentiating bacterial infections from viral or inflammatory diseases, reducing unnecessary antibiotic use, and development of resistance.[2]

A true, accurate diagnosis builds the cornerstone to saving lives in the many infectious diseases that can lead to the development of sepsis. In view of the enormous array of biomarkers available, procalcitonin (PCT) has proven its effectiveness in both diagnostic and prognostic capacity. However, it is upregulated during systemic bacterial infections and thus functions ideally as a biomarker for bacterial infections. In terms of usefulness for the infection-management spectrum, PCT can be utilized for early diagnosis and optimizing antibiotic therapy. Procalcitonin is synthesized primarily by the C-cells of the thyroid gland under normal conditions. However, procalcitonin is produced in larger amounts during infections, especially of bacterial origin, by various tissues and organs. This upregulation is driven by pro-inflammatory cytokines, particularly in response to bacterial endotoxins such as lipopolysaccharides(LPS). In contrast, viral infections tend to suppress procalcitonin production through interferon-gamma, making PCT a useful discriminator

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between bacterial and viral infections. Procalcitonin cleaves to calcitonin; thus, during infection, cleavage is incomplete, and procalcitonin is released into the bloodstream. Levels of PCT rise significantly within two to six hours and peak within 12-24 hours upon the onset of the infection, rendering it an early marker for systemic bacterial infection.

Beyond its use in sepsis, PCT has also been shown to be useful in the management of other conditions, such as lower respiratory tract infections (LRTIs) and urinary tract infections (UTIs). Recent investigations have studied its role in critically ill patients, revealing that serial procalcitonin readings can provide significant prognostic information and guide therapeutic decisions.[3,4]

The Physiology of Procalcitonin

Thyroid C-cells produce tiny amounts of procalcitonin, which is converted to calcitonin under normal physiological settings, and plays a role in calcium homeostasis.[5] Procalcitonin is a large, 116-amino acid peptide precursor of the hormone calcitonin, which interplays intensely with calcium homeostasis,In reaction to microbial poisons and certain cytokines, such as interleukin, parenchymal cells release PCT widely. On the other hand, several cytokines produced in reaction to a viral infection, especially interferon-γ, reduce the generation of PCT.Despite the lack of clarity surrounding PCT's precise downstream effects, preclinical research shows that PCT plays.[6]During bacterial infection, PCT is produced in large amounts by all organs and cell types, including hepatocytes and adipocytes, in response to IL-1β and TNF-α.[7] Interestingly, viral illnesses stimulate interferon-gamma synthesis, which suppresses procalcitonin production, providing the first mechanism for PCT in differentiating bacterial from viral infections.[8]To identify individuals at risk of clinical deterioration to septic shock, multiorgan failure, and other conditions, a high degree of suspicion is essential. By early detection of older individuals with severe infections, biomarkers like PCT may improve sepsis management in these time-sensitive decisions.[6]

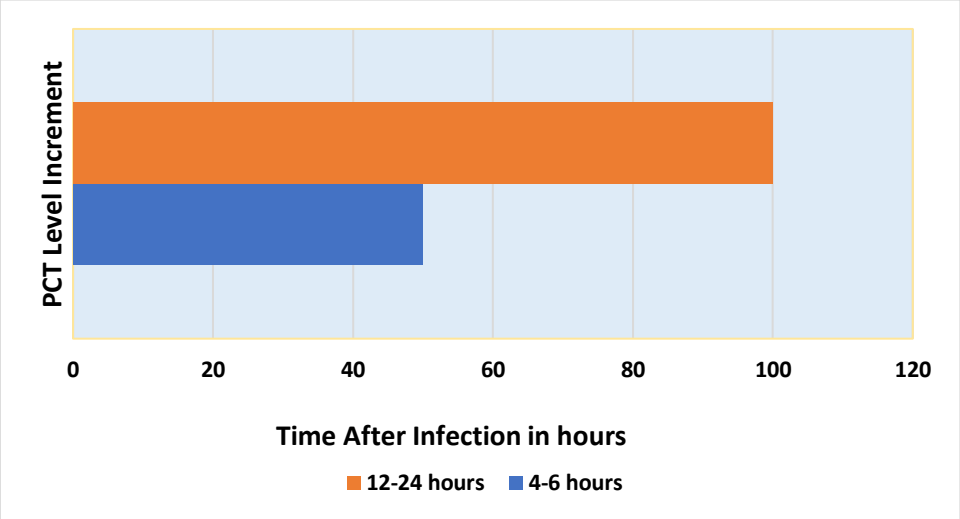

Figure 1: Procalcitonin response time in bacterial infections

Procalcitonin is a reliable early indicator of systemic bacterial infections, particularly sepsis, due to its rapid elevation in response to bacterial endotoxins.[9]Studies demonstrate that PCT levels increase within 4-6 hours of infection initiation and reach their peak within 12-24 hours, but established markers like CRP may take longer to rise.[10]This quick response time is critical in diseases like sepsis, when early detection and treatment can greatly improve outcomes.During inflammation and sepsis, PCT is produced by a completely distinct mechanism (figure 1),the details of which are unknown. Several investigations have demonstrated that PCT is produced in response to bacterial lipopolysaccharide (LPS) or other endotoxins, as well as inflammatory indicatorssuch as IL-β, IL-6, TNF-α, and IL-2.[11]

Procalcitonin as a Diagnostic Biomarker

Procalcitoninused as a diagnostic biomarker has been validated in a variety of clinical settings. The capacity to distinguish between bacterial and viral infections has led to its widespread usage in settings like emergency departments, intensive care units (ICUs), and primary care clinics.[12,13]Sepsis is one of the most important applications of PCT is the identification of sepsis, a life-threatening illness caused by an abnormal immunological response to infection. PCT is superior to other measures such as CRP and white blood cell count (WBC) for sepsis diagnosis because of its specificity for bacterial infections.[14]Meta-analyses show that procalcitonin has high diagnostic accuracy in diagnosing sepsis, with sensitivity and specificity sometimes surpassing 80% as seen in figure 2.[15]

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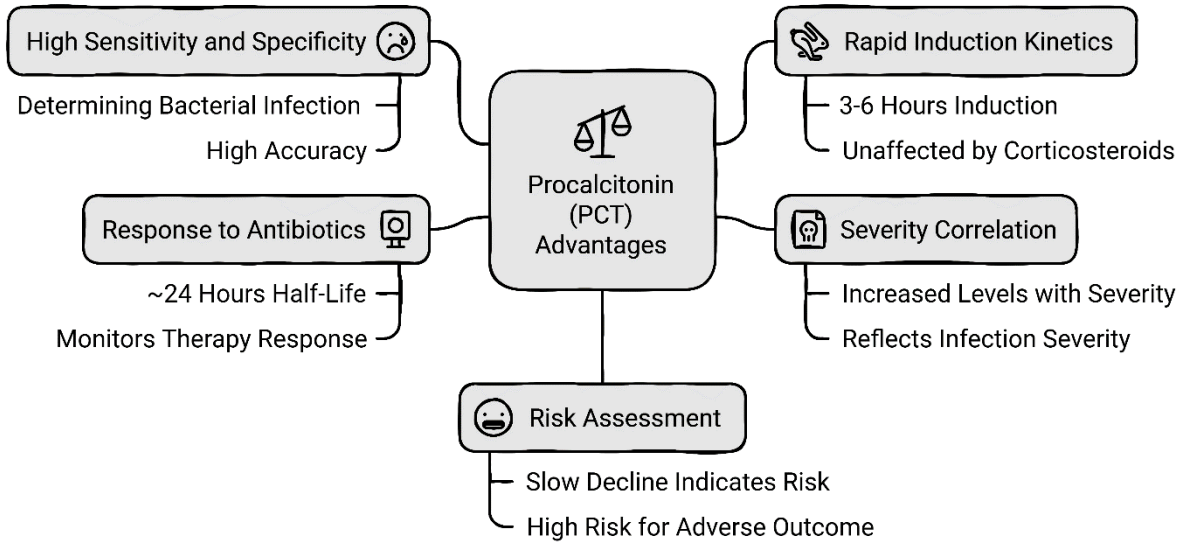

Figure 2: Clinical advantages of PCT

Respiratory tract infections: The use of PCT has been established as effective in differentiating between bacterial and viral infections in patients with lower respiratory tract infections (LRTIs). Numerous studies have demonstrated that in pneumonia or COPD exacerbations, a PCT-based approach for the beginning and termination of antibiotics can successfully restrict antibiotic administration without losing optimal patient outcomes.[16–18]Conventional diagnostic markers like blood cultures and C-reactive protein have significant limitations. Patients with a clinical suspicion of infection may have inferior sensitivity and specificity when measuring CRP (protein).[10]In pediatric populations, where distinguishing between bacterial and viral infections can be difficult, PCT has been investigated as a marker to help guide the therapy of febrile urinary tract infections. PCT levels correspond with the probability of renal involvement, allowing doctors to make educated decisions regarding the use of antibiotics and imagng.[18]

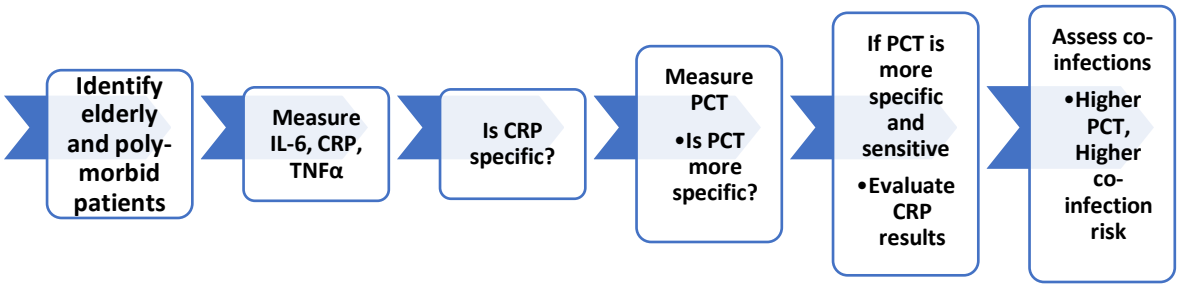

Figure 3: The cascade of assessment of infection through PCT

Procalcitonin as a therapeutic marker

When doctors used PCT to make clinical decisions about infections, they considered it helpful, especially when they described the results as "very high" or "low," rather than according to "middle values". The doctors thought PCT was beneficial for cancer patients. Clinical judgments were frequently seen as difficult in these situations because the fever, compromisedgeneral illness or elevated CRP may be related to an infection or cancer. "In cancer patients, elevated CRP does not always indicate an infection; in these situations, PCT is a useful tool to get a comprehensive picture ".[19]

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Procalcitonin's clinical relevance extends beyond diagnosis, including prognosis, therapy monitoring, and antibiotic stewardship.[20]Studies have shown that dynamic variations in PCT levels might guide therapeutic measures and predict outcomes in critically ill patients.[21]Procalcitonin is widely used for antibiotic stewardship, reducing needless antibiotic use and combating antimicrobial resistance. Procalcitonin-guided algorithms have been found to reduce antibiotic use in both inpatient and outpatient settings while not increasing the risk of adverse events. For example, in a landmark randomized controlled trial (ProHOSP), patients with lower respiratory tract infections who were treated using a PCT-guided strategy had significantly decreased antibiotic exposure compared to those treated with standard recommendations.[13]

Procalcitonin is more specific to bacterial infections than other indicators. It tends to rise in response to bacterial infections, particularly sepsis while remaining relatively low in viral infections or inflammatory illnesses such as autoimmune diseases.CRP, ESR (erythrocyte sedimentation rate), and WBC (white blood cells) levels are high in a wide range of inflammatory illnesses (bacterial and viral infections, trauma, and autoimmune diseases), rendering them less specific to bacterial infections.Procalcitonin levels can also be used as a prognostic indicator in patients with severe infections. In sepsis, consistently high or growing PCT levels are associated with worse outcomes, including increased death.[3]A quick reduction in PCT levels is associated with a better prognosis.[22]During the COVID-19 pandemic, PCT was investigated as a possible marker for separating COVID-19-related pneumonia from bacterial co-infection. Research indicates that patients with COVID-19 pneumonia typically have low PCT levels, allowing doctors to avoid unnecessary antibiotic administration.[23] However, in cases of subsequent bacterial illness, higher PCT levels may suggest the need for antibiotics.[24]

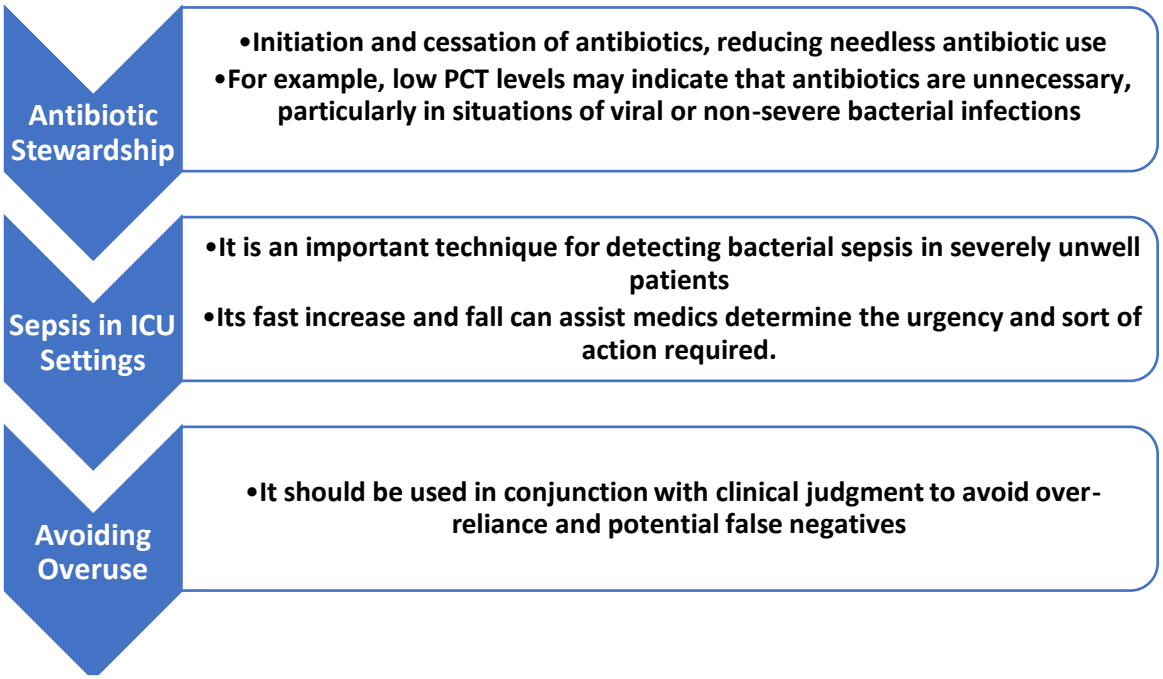

Figure 4: Judicious uses of Procalcitonin

One of the cost-cutting strategies investigated is the use of Procalcitonin (PCT) as a biomarker to guide antibiotic therapy.Recent research has revealed encouraging findings about the cost savings and cost-effectiveness of procalcitonin testing, although in many contexts and patient populations, including hospitalized patients with respiratory tract infections or patients with critical infections PCT can assist clinicians in determining whether to initiate or terminate antibiotic therapy, particularly in sepsis care. By providing early indicators of bacterial infection severity, PCT-guided methods assist reduce unnecessary antibiotic use, lowering medicine costs, and reducing the possibility of antibiotic resistance.[25]

PCT-guided therapy has shown to be a cost-effective strategy in India. While initial testing may be costly, it is often offset by savings from reduced antibiotic consumption and shorter ICU stays. This makes PCT a viable technique in cost-constrained countries such as India, aligning with the larger goal of providing high-quality yet economical critical care.One of the cost-saving measures.[26]When determining when to begin antibiotic therapy in septic patients, the current sepsis guideline advises against using PCT and clinical evaluation. More studiesare required in this area, particularly to compare protocols based on a fixed value (i.e., 0.5 ng/mL as cut-off) to PCT kinetics (i.e., changes in 12–24 hours). Additionally, the

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higher incidence of recurring infections, the distinction between patients undergoing surgery and those receiving medical care, and ultimately the question of whether a conservative or liberal regimen is more advantageous should all be the subject of additional research.[27]

Limitations of Procalcitonin

Despite its clinical usefulness, PCT has its limits. Certain situations, such as acute trauma, surgery, and malignancies, might boost procalcitonin levels in the absence of bacterial infection, resulting in probable false positives.[28]Similarly, localized bacterial infections, such as abscesses or endocarditis, may not necessarily induce a systemic procalcitonin response, leading to false negatives.In line with the earlier meta-analysis in septic patients, a higher infection recurrence rate did not lead to an increased ICU (intensive care unit) and in-hospital stay in the PCT group.[27]Although PCT testing is widely available, it is still more expensive than standard serum indicators such as CRP or WBC count.

Future Directions and Research

Procalcitonin research is evolving, with ongoing investigations addressing its role in new clinical contexts and its combination with other biomarkers for greater diagnostic precision [7]. PCT is being explored for its involvement in non-infectious inflammatory illnesses such as acute pancreatitis, trauma, and heart surgery.[29]

A recent study suggests that combining PCT with other biomarkers, such as IL-6 or soluble urokinase plasminogen activator receptor (suPAR), can increase diagnosis accuracy in sepsis.[30]multi-biomarker panels can provide a full picture of a patient's state, enabling more personalized and precise treatment.[31]Advancements in point-of-care testing (POCT) have made procalcitonin measurement more accessible in emergency and outpatient settings. Rapid PCT assays that offer answers within minutes should help clinical decision-making, particularly in time-sensitive diseases like sepsis.[32]

CONCLUSION

Prozalcitonin has emerged as an important biomarker in the detection and treatment of bacterial infections. The ability of it to differentiate between bacterial and viral illnesses makes it a vital tool in the age of antibiotic resistance. Procalcitonin plays an important role in antibiotic stewardship programs by promoting rational antibiotic use and reducing inappropriate antimicrobial exposure. Procalcitonin's potential usefulness in infectious and non-infectious illnesses may expand with further research.When compared to standard care, a daily PCT-guided strategy results in a considerable safe reduction of total antibiotic days in critically sick hospitalized individuals with sepsis.Early identification and antibiotic treatment are crucial for sepsis management. Once treatment is started, frequent monitoring is done by identifying individuals with a favorable clinical course and minimal risk of sequelae is crucial for deciding whether to discontinue antibiotic treatment. This would strengthen the use of this marker in real-world practice.

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