RESEARCH PAPER

Elevated Procalcitonin in Gram-Negative Bacteraemia: Diagnostic Precision Over Conventional Markers

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Abstract

Gram negative bacteraemia continues to be a significant cause of sepsis, demanding early and precise diagnostic intervention. Traditional biomarkers such as white blood cell count and C-reactive protein are not precise enough to discriminate between various types of pathogens and often fail to assist early clinical decisions. Procalcitonin (PCT), a precursor of calcitonin, has emerged as a promising biomarker as it can be rapidly elevated in response to bacterial endotoxin and host mediated inflammatory cytokines. This study emphasizes the diagnostic and prognostic value of PCT in Gram negative bacterial infection, highlighting its efficiency over conventional markers in differentiating bacterial from viral infection in its early stage. Elevated PCT levels are significantly induced by Gram negative bacterial infection owing to its activation of Toll like receptor pathway followed by cytokine release. In summary, this review portrays the diagnostic accuracy, molecular mechanism and clinical significance of PCT in the clinical setting for early disease intervention.

Keywords: PCT, Gram negative bacteraemia, early screening, diagnostic accuracy

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1. Introduction

Gram-negative (GN) bacteremia-driven bacterial sepsis is progressively a concern as a major global health emergency, compromising millions of lives each year through septic shock and antimicrobial resistance. Elevated procalcitonin (PCT) has been explored as a pivotal biomarker in the occurrence of bloodstream infections, particularly in discriminating gram-negative from gram-positive or fungal bacteraemia. In conventional settings C-reactive protein (CRP) and total leukocyte count provide limited insight to diagnose and discriminate between various pathogen classes including their distinct etiologies capping early clinical prognosis. Procalcitonin (PCT) is the precursor to calcitonin, has a molecular weight of 13 kDa and is made up of 116 amino acids. Three distinct molecules are formed as the preliminary peptide undergoes a sequence of splits in the neuroendocrine cells of the thyroid gland, lung, and pancreas, resulting in the formation of three separate molecules: 32 amino acids containing calcitonin, 21 amino acids containing katacalcin, and 57 amino acids containing N-terminal fragment aminoprocalcitonin. In 1993, Assicot gave the initial observation of elevated serum PCT levels in sepsis patients. Given the challenges of diagnosing infections in critically ill patients and those experiencing sepsis-induced shock, an easily accessible and cost-effective biological marker for infection would be valuable. According to recent studies, high levels of procalcitonin (PCT) in the serum occur during bacterial and fungal infections in the

*Author for Correspondence: sriparnade2@gmail.com absence of mature calcitonin, while PCT levels remain low in cases of viral infection. (Carrol et al., 2002) (Powell et al., 2023)

According to Cabral et al, the PCT value is elevated for the Gram-negative (GN) bacteria compared with sepsis caused by bacteria with Gram Positive (GP) characteristics (Cabral et al., 2019). The variation was most noticeable when the causal agents were Enterobacteriaceae rods, such as *Escherichia coli* or *Klebsiella pneumoniae*, or glucose non-fermenting bacilli, including *Pseudomonas* spp. and *Acinetobacter* (Cabral et al., 2019). In critically sick and haematological patients, high PCT levels have been correlated with bacteraemia, particularly GN bacteraemia, compared to GP bacterial and fungal infections. Additionally, it has been reported that the frequency of GN bacterial infection is significantly higher in patients with septic shock in the critical care unit than in patients with sepsis or severe sepsis. Serum PCT levels were significantly higher in GN sepsis than in GP sepsis, while serum CRP levels were similar between the GN and GP sepsis groups. PCT levels are significantly elevated both in vitro and in vivo when lipopolysaccharide (LPS) is induced. The prevalent production of PCT during infections is caused either directly by microbial toxins such as endotoxin LPS or it is caused indirectly by humoral triggers or the cell-mediated host response. Tumor necrosis factor-alpha, interleukin-1, interleukin-6, and other powerful effector cytokines are produced when LPS activates mononuclear cells through the related "toll-like receptor" protein 4, and in turn PCT is released from different cell lines when cytokines are triggered in the body system (H. H. Liu et al., 2017). Procalcitonin levels are often lower in TB because the inflammatory response is often more localized and less intense. On the other hand, bacterial pneumonia typically results in a strong pro-inflammatory response from the host immune system, which releases cytokines and other mediators that promote the synthesis of procalcitonin (Abdullah Fikri et al., 2025a) (H. H. Liu et al., 2015a).

The diagnostic precision of elevated procalcitonin both as a significant threshold and in combination with other laboratory indices, proclaims a promising avenue to ameliorate the early identification of gram-negative bacteremia. Conventional markers such as CRP and white-blood-cell count often fail to reliably differentiate between gram-negative and gram-positive bacteremia, as their elevations can mitigate viral, non-infectious systemic inflammation, and even in some fungal infections. This lack of microbial specificity increases the risk of inappropriate empirical antibiotic adaptation and precise treatment protocol for critically ill patients impeding clinical decision making. Hitherto, this review aims to evaluate how PCT conquers conventional markers in diagnostic accuracy, early screening and treatment planning of antimicrobial therapeutics against gram-negative bloodstream infections.

2. Physiological role of PCT

A bacterial infection raises serum PCT levels, whereas levels remain stable or very slightly rise in a non-infection state. However, there was no statistically significant difference between fungal and Gram-positive bacterial infections, but the concentration of PCT among individuals with GN bacterial infection was significantly greater than that of the GP bacterial infection and fungal infection group (Tang et al., 2018a). Thyroid C cells constitutively generate PCT regardless of hormonal activity, and it rises in reaction to gastrin and hypercalcemia. Before being released into the bloodstream, PCT is usually divided into calcitonin and the N-terminal residue. However, when bacterial endotoxins (LPS) or inflammatory cytokines like TNF-α, IL-6 and IL-1β are present, the production of PCT increases significantly, up to 100–1000 times. When it comes to sepsis and infection, PCT has the most effective sensitivity and specificity. It is well established that various Toll-like receptor (TLR) signalling pathways are activated by GP and GN bacteria or fungi. As a result of this, systemic pro-inflammatory cytokines are produced at higher levels, which cause PCT to be released (un Nisa et al., 2024).

PCT levels in patients' blood are distinguished by the species of bacteria found in blood cultures and the isolation of bacteria. Blood culture-positive subjects had substantially greater PCT concentrations than blood culture-negative cases. Furthermore, patients with *E. coli* or K. pneumoniae infections had significantly higher PCT concentrations than patients with S. epidermidis and GP cocci other than *S. aureus* and *S. epidermidis*, although there was no significantly discernible difference between *S. aureus* infected patients and any other patients. Patients carrying GN rods had greater PCT concentrations overall than those harbouring GP cocci. Additionally, we discovered that, in comparison to instances caused by non-ESBL-producing bacteria, ESBL-producing bacteremia cases caused by *Proteus mirabilis* and *E. coli* had greater PCT concentrations (Seki et al., 2016). When considering GN (GN) and GP (GP) bacteria, notable distinctions exist between the various types of sepsis. Procalcitonin (PCT) is typically found at normal levels in patient populations without infection, and it seems to be more dependable than many other biomarkers in individuals suspected of having a bacterial infection.

There are two main ways that procalcitonin is produced in many organs, including the lung, liver, kidney, and adipose tissue, during systemic inflammation, especially in bacterial infections (Suberviola et al., 2012). While inflammatory mediators like TNF-α and IL-6 stimulate the indirect pathway, lipopolysaccharides (LPS) or similar detrimental bacterial metabolites initiate the direct pathway (Vijayan et al., 2017a). Although the precise mmechanism by which procalcitonin is produced during infection is yet unknown, it is thought that sepsis-induced cytokines and bacterial LPS affect the generation of procalcitonin by peripheral blood mononuclear cells and liver (Bosmann & Ward, 2013). In accordance with the severity and mortality of the illness, increased CALC-1 gene expression caused by microbial infections can lead to a 1,000-fold increase in procalcitonin production.

2.1 Biosynthesis and Physiological Origin of PCT

2.1.1 CALC-1 gene expression:

The calcitonin gene-1 (CALC-1) on the human 11th chromosome directs the synthesis of procalcitonin. In healthy conditions, the thyroidal synthesis of PCT is done by parafollicular cells (C cells) in the thyroid gland and in trace amounts by K cells in the lung. During any pathological conditions of the body, parenchymal cells and leukocytes can also produce procalcitonin via CALC-1 gene regulation. Extra thyroidal CALC1 gene transcription is blocked and PCT synthesis is limited in C cells. The CALC-1 gene comprises five introns, six exons, and a promoter region that has many inflammatory transcription factor consensus sites. Preprocalcitonin (141 amino acids) and calcitonin gene-related peptide (CGRP) are the two specific transcripts produced by alternative splicing of the CALC-1 gene. Following translation, preprocalcitonin proceeds to the endoplasmic reticulum, where it is broken down, resulting in PCT generation (Matur et al., 2017).

In the normal physiological conditions, β-adrenergic stimulation, hypercalcemia, increased levels of glucocorticoids, glucagon, calcitonin gene-related peptide and gastrin promote the activation of C cell, while somatostatin and vit. D repress it (Matur et al., 2017a).

2.1.2 Tissue-specific production under normal conditions

The 141 amino acids chain of preprocalcitonin is the original product of the CALC-I gene, which produces PCT in thyroid C-cells and perhaps also during inflammation. The signalling region at the N-terminus with its hydrophobic characteristics facilitates binding to the endoplasmic reticulum where it is broken by endopeptidase, giving rise to PCT. Calcitonin is produced by cleaving PCT at its N-terminal sequence and the C-terminal fragment (catacalcin) inside the C-cells. After the formation of its secondary and tertiary structures, calcitonin is released into the bloodstream. Two cysteine remnants in positions 1 and 7 form a disulfidic bridge and the C-terminus proline is hydroxylated. Both structures, needed for the binding of calcitonin to its receptor, are therefore not a part of the PCT structure and are only created after the calcitonin has been cleaved from PCT. Practically all of PCT generated in C-cells is converted into calcitonin, such that no PCT reaches the circulation and its levels in healthy patients are below the detection level. The circulating PCT cannot be broken down by any enzymes in the plasma. In contrast to calcitonin, which has a half-life of 4–5 minutes, PCT has a half-life of 25–30 hours if it manages to evade intracellular proteolysis and is secreted into the circulation (Tang et al., 2018b).

2.1.3 Processing of PCT to calcitonin

Under normal circumstances, the thyroid gland C cells create procalcitonin, which is the precursor to the hormone calcitonin. Additionally, leukocytes in pathological conditions and parenchymal cells of many organs create it. Under normal circumstances, some enzymes transform procalcitonin into calcitonin. As a result, there is very little of it in circulation. Conversely, because parenchymal cells' procalcitonin cannot be transformed into calcitonin, it rises in the blood and tissue during illnesses. Procalcitonin in humans under both healthy and pathological settings has been extensively studied (Matur et al., 2017b). The CALC-1 gene encodes PCT, which serves as a precursor to the hormone calcitonin. It first comes from pre-procalcitonin, which has 141 amino acids. A 116 amino acid long PCT is produced following the elimination of the signal peptide with amino acids 1–25. The N-terminal fragment with 57 amino acids, calcitonin with 32 amino acids, and katacalcin with 21 amino acids, are its three portions. PCT is a member of the CAPA peptides family, which also contains amylin, adrenomedullin, calcitonin, and calcitonin gene-related peptides I and II. (Nakagawa et al., 2024a).

The human 11th chromosome's calcitonin gene-1 (CALC-1) controls the generation of procalcitonin (Becker et al., 2010). The CALC-1 gene consists of six exons, five introns, and a promoter region containing several consensus sites for inflammatory transcription factors. Calcitonin gene-related peptide (CGRP) and preprocalcitonin, which consists of 141 amino acids, are two different transcripts that are generated by alternative splicing of the CALC-I gene. Signal peptide, which has 25 amino acids, and PCT, which has 116 amino acids, make up preprocalcitonin. After translation, preprocalcitonin travels to the endoplasmic reticulum, where the signal peptide is broken down to produce PCT. Three peptide products are then released when PCT is broken down by certain endopeptidases: N-procalcitonin, which has 57 amino acids; calcitonin, which has 32 amino acids; and katacalcin, which has 21 amino acids. (Le Moullec et al., 1984). N-procalcitonin has been found in certain hypothalamic areas that are crucial for controlling eating and energy balance, as well as in adipocytes and neuroendocrine cells. (Tavares et al., 2007). Calcitonin opposes parathyroid hormone and is involved in the metabolism of calcium and phosphorus. (COPP & CHENEY, 1962)

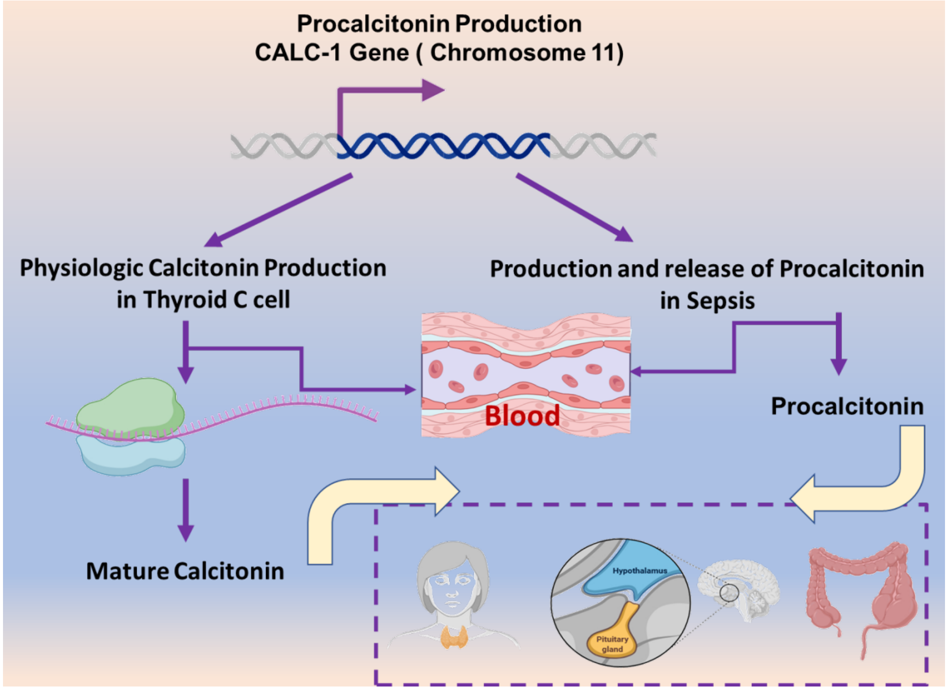

Figure 1. Schematic pathophysiological impact of Procalcitonin during bacterial sepsis

2.1.4 Pathogen-associated molecular patterns (PAMPs)

Diverse pathogens have distinct virulence mechanisms that trigger diverse host inflammatory reactions, and variations in these pathogens' particular signalling result in varying serum PCT amounts (Xu et al., 2022). GN bacteria contain LPS, while GP bacteria include lipoteichoic acid (LTA). Through pattern recognition receptors, the innate immune system identifies LPS and LTA as pathogen-associated molecular patterns (PAMPs), which can initiate signalling pathways and result in the production of pro-inflammatory cytokines. Members of the Toll-like receptor (TLR) and C-type lectin receptor (CLR) families are examples of pattern-recognition receptors. (Xu et al., 2022). Most TLRs are essential for identifying microorganisms. Pro-inflammatory cytokines are released when PAMPs bind to TLRs, starting signalling cascades. TLR4 detects LPS as a ligand, while TLR2 detects PGN. When LPS binds to TLR4, it induces the traditional MyD88-dependent signalling pathway and causes the release of cytokines including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (Li et al., 2016a).

In vitro, distinct inflammatory cytokines and leukocyte gene expression patterns are induced by the dominant activation of TLR4 by Gram negative bacteria and the dominant activation of TLR2 by Gram positive bacteria. Strong inflammatory cytokines, such as IL-1, TNF-alpha, and IL-6, are released when TLR4 is activated. These cytokines stimulate gene transcription, enhance PCT secretion by organs other than the thyroid gland, and produce a sharp rise in serum PCT levels. However, TLR2 activation has an indirect and comparatively mild stimulating effect on cytokine release, which results in a negligible rise in PCT levels (Xu et al., 2022). TLR4/myeloid differentiation factor-2 (MD-2) ligands were predominant in E. coli and K. pneumonia. These bacteria greatly mimicked TLR4/MD-2-expressing cells and raised PCT levels.) (Li et al., 2016b).

2.1.5 Endotoxin (LPS)-mediated signalling pathways

The role of toll-like receptors in the whole blood response to various bacterial infections varied greatly and it depended on the composition of bacterial outer membranes, which are one of the main determinants of the Gram character. As a result, the invading pathogen determined the magnitude of the cytokine response. In particular, it has been demonstrated that TNF-α plays a vital and extremely proximal role in the cytokine response to bacteria; nevertheless, independent of the causal bacterium, plasma TNF-α is not always high. Given that this cytokine plays a crucial part in the release of PCT from different cell types during a systemic bacterial infection, the pathogen's traits may be at least partially responsible for the degree of PCT increase. It has been demonstrated in vitro that the supernatants of cultivated human cells stimulated by LPS had a considerably greater PCT peak value than those stimulated with muramyl dipeptide, which is a part of the cell wall of Gram-positive bacteria. (Charles et al., 2008)

In healthy individuals, PCT levels are extremely low and nearly undetectable (<0.0025 Ug/ml). The body releases several inflammatory cytokines in response to severe injury and infection, which causes subsequent damage to tissues and organs. PCT is constantly released by septicopyemia patients, which causes the systemic inflammatory response syndrome. According to correlational research, PCT can be found two hours after a general bacterial infection, increases quickly within six hours, and peaks about twenty-four hours later. As a result, it offers a foundation for septicopyemia early identification and warning. The Gram-negative bacterial infection group in this study had significantly increased

PCT levels than the Gram-positive bacterial infection group (Gao et al., 2017)

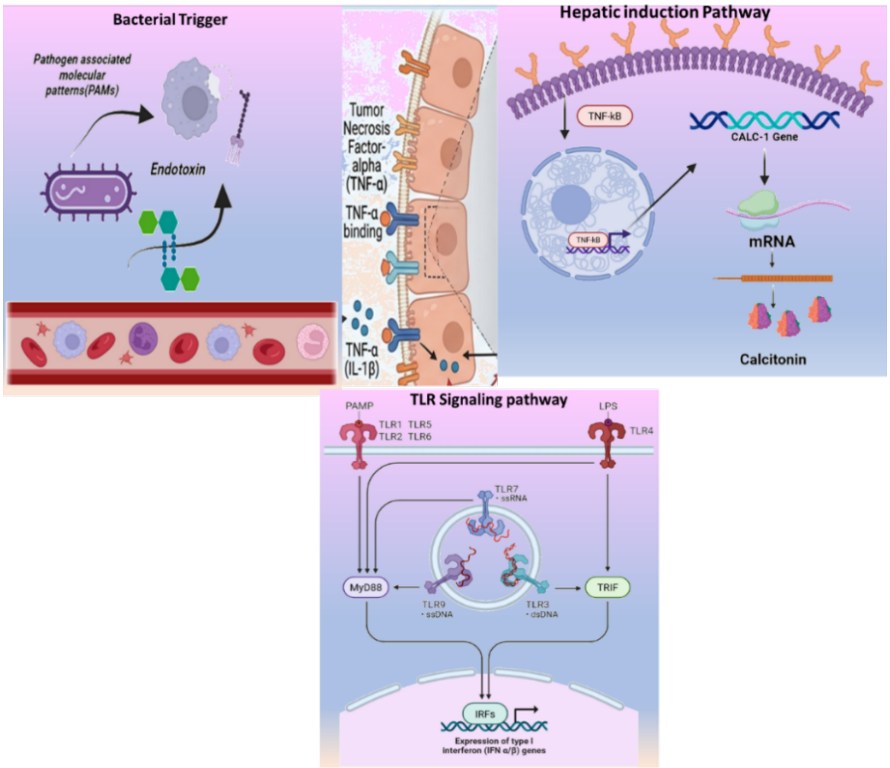

Figure 2. Molecular insight perspectives of PCT induced bacterial infection.

2.1.6 Cytokine-Driven Regulation of PCT Expression

Hypersensitivity due to infection causes the elevation of the inflammatory marker PCT. The cytokine cascade, which is crucial to the pathophysiology of this severe hypersensitive reaction, may be connected to the precise process of PCT synthesis during anaphylaxis. The production of cytokines, including tumor necrosis factor-alpha (TNF-α), IL-6, IL-10, and others, which have been reported to be higher in severe anaphylactic responses, further intensifies PCT synthesis. During systemic inflation condition of bacterial infection or anaphylaxis, non-thyroid tissue starts the production of PCT through an alternative signalling pathway. While cytokines like IL-6 and TNF receptor I increase later in anaphylaxis, mediators like histamine and mast cell tryptase peak immediately, coinciding temporally with the possible activation of alternate pathways for PCT synthesis. IL-6 acts as a synergistic activator of the Calc-1 promoter, responsible for the transcription of PCT (Bánvölgyi et al., 2025).

During infection caused by bacteria, the lipopolysaccharide layer of Gram-negative bacterial cell wall triggers monocytes to release IL-6 within 3 hours. IL-6 then stimulates JAK/STAT as well as NF-κB pathways to upregulate CALC1 gene transcription in leukocytes, liver cells and other non-thyroid cells. Research shows that IL-6 operates in association with TNF-α and IL-1β to increase PCT 100–1000 times above normal (Zeng et al., 2022). IL-1β is another factor that regulates PCT expression during bacterial infection, as it activates monocytes during the infection stages. Bacterial exotoxin and LPS layer as endotoxin, stimulate macrophages to secrete IL-1β using caspase-1 cleavage and NLRP3 inflammasome mechanism. IL-1R1 binds with IL-1β, initiating NF-κB and MAPK pathways that enhance CALC-1 transcription in lung, liver, and adipose tissues that are devoid of the enzyme responsible for PCT synthesis. This forms a mature PCT peptide that increases 100–1000 times in 3–6 hours of the infection and works in the same manner as TNF-α and IL-6 (Becze, 2016a). LPS endotoxin triggers macrophages and other monocytes to synthesis TNF-α through TNFR1 signaling. Following TNF-α binding to TNFR1 on non-thyroidal tissues like liver, lungs, kidneys, and adipocytes. TNF-α causes NF-κB translocation and MAPK/AP-1 activation for CALC1 activation, responsible for synthesis mature PCT (Gregoriano et al., 2020).

PCT is derived from the CALC-1 gene, which is often activated in extrathyroidal tissues by bacterial stimuli, such as LPS, and cytokines like IL-1β/IL-6/TNF-α through the NF-κB signalling pathway. In the case of viral infection, different viral components such as dsRNA is recognized and NK cells, T cells, and macrophages release IFN-γ that binds IFNGR1/IFNGR2 receptors. This triggers SOCS1/3 and IRF-1 transcription factors that suppress CALC-1 promoter activity by activating JAK1/JAK2-STAT1 signalling. Additionally, IFN-γ prevents NF-κB translocation, which stops PCT transcription upon viral infection (Kang et al., 2018).

2.1.7 PCT as an Inflammation-Responsive Peptide

Procalcitonin synthesis in physiological and pathological conditions is controlled by the CALC-1 gene (H. H. Liu et al., 2015b). It is secreted by C cells (parafollicular cells) of the thyroid gland, and trace amounts are produced by K cells in the lung under physiologic conditions, which is called neuroendocrine or thyroidal production. In pathological states, it is formed in parenchymal and leukocytic elements, which is called extra thyroidal production. Under normal circumstances, PCT is produced by C cells and transforms into the mature calcitonin hormone, which is then stored in secretory granules and released upon suitable stimulation (Müller et al., 2001). In the meantime, PCT synthesis in C cells is limited and extra-thyroidal transcription of the CALC I gene is repressed (Christ-Crain & Müller, 2007). In physiological settings, C-cells are stimulated by hypercalcemia, β-adrenergic stimulation, increased glucagon, glucocorticoids, and gastrin. On the other hand, somatostatin and vitamin D inhibit C cells (Maruna, P, Nedelnı kova , K, & Gu rlich, R. (2000). Physiology and genetics of procalcitonin. *Physiological Research, 49*, (Suppl 1), S57-S61.).

2.1.8 Extra-thyroidal mechanism of PCT

During severe bacterial infections or inflammation, parenchymal cells produce PCT. Another term for procalcitonin is *hormokin*. Similar to hormones, it is produced by endocrine glands under physiological settings, but like cytokines, it is secreted in significant quantities by different tissues during inflammation (Christ-Crain & Müller, 2007). The main extra-thyroidal PCT production sites include the small intestine, pancreas, liver, spleen, kidneys, adrenal gland, lung, brain, spinal cord, stomach, testes, colon visceral fat, skin, peritoneal macrophages, and leukocytes (Müller et al., 2001). Serum PCT levels have been seen to rise following LPS injection, which supports extra-thyroidal production.

Endopeptidases break down the procalcitonin produced in C cells into peptides like katacalcin or calcitonin. Because parenchymal tissues lack this enzyme, the produced prohormone is released into the bloodstream as PCT without undergoing any degradation (Linscheid et al., 2003a). Consequently, whereas calcitonin levels do not significantly alter, procalcitonin levels noticeably rise in a short period of time (Niemirowicz et al., 2016). One of the extra-thyroidal locations where PCT is generated is in leukocytes. During infections, it is first secreted in trace amounts by neutrophils and then by tissue macrophages (Meisner, 2014). Macrophages enhance the release of tissue PCT, but tissue PCT is released even in the absence of macrophages (Linscheid et al., 2003b). Procalcitonin is regarded as an immune system component since inflammatory cytokines, including IL-1β, IL-6 and TNF-α also affect its release. However, the greater PCT mRNA increase and PCT peptide release from parenchymal cells compared to circulating cells following an infection suggest a tissue-based rather than leukocyte-based host defense mechanism (H. H. Liu et al., 2015b). It was discovered that PCT prevented lymphocytes from producing prostaglandins in vitro when exposed to arachidonic acid. Arachidonic acid and prostaglandins both maintain homeostatic processes and mediate pathogenic processes, such as the inflammatory response (Ricciotti & FitzGerald, 2011).

2.1.9 Induction by pro-inflammatory cytokines:

In bacterial infections or sepsis, PCT production is increased by both LPS from the GN bacterial cell wall and inflammatory cytokines such as IL-6, IL-1β and tumor necrosis factor-alpha (TNF-α). These cytokines increase the transcription of the CALC-1 gene, which causes the release of PCT. In fact, it has been suggested that stimulus-specific response regions within the promoter gene regulate this sepsis-related increase in CALC-I gene transcription (Domenech et al., 2001). PCT may rise in certain clinical circumstances other than bacterial infections. Tumors are among the most prevalent conditions in humans. PCT levels are elevated by lung small cell carcinoma, bronchial carcinoma, thyroid gland medullary carcinoma, and neuroendocrine tumors of the gastrointestinal tract. PCT production in extra-thyroidal tissue is also increased by severe non-infectious inflammatory stimuli, such as acute multiorgan failure, major burns, acute sterile pancreatitis, severe trauma, or major abdominal or cardiothoracic surgery (Becze, 2016b). Kawasaki disease (Okada et al., 2004), graft-versus-host disease (aGvHD), T-cell antibody infusion (Dornbusch et al., 2008) and heatstroke (S & M, 2013). The released amount of procalcitonin is a significant diagnostic marker towards the bacterial presence and its classification. Compared to GP bacteria, GN bacteria trigger the secretion of PCT. The underlying cause is that GP bacteria particularly activate the Toll-like receptor-2 pathway, while gram-negative bacteria activate the Toll-like receptor-4 (TLR-4) pathway. This leads to distinct inflammatory cytokine production, which in turn stimulates the ubiquitous transcription of calcitonin mRNA and the release of PCT from various tissues.
(Leli et al., 2015a).

The inhibiting effects of IFN-γ and IL-17 are overcome by mixed infections generated by both bacterial and fungal pathogens. As a result, when bacterial and fungal diseases coexist, PCT levels rise. However, compared to bacterial infections, this elevation is lower (Becze, 2016c). The smooth muscles of the arteries may potentially be impacted by procalcitonin. In vitro, procalcitonin prevented lymphocytes from producing thromboxane (Meisner, M., Scholer, A., Tschaikowsky, K. & Schu ttler, J. (1996). Procalcitonin inhibits camp, prostaglandin E and thromboxane B-production of human lymphocytes. *Acta Anaesthesiologica Scandinavica, 44*, 251-252.). Heart stroke may be influenced by the relaxation of vascular muscles brought on by the inhibition of the vasoconstrictor thromboxane. Indeed, PCT was found to induce a slight vasodilator response in pigs' coronary arteries (Wei et al., 2008). Conversely, PCT inhibited the cytokine-induced nitric oxide synthesis gene in smooth muscle cells in vitro. In cases of severe sepsis and septic shock, this may represent a counterregulatory mechanism aimed at the high nitric oxide generation and the accompanying systemic hypotension.

2.1.10 Difference between viral & bacterial infections

Similar symptoms, including fever, muscle soreness, and weakness, are caused by both bacterial and viral infections. Appropriate treatment and prognosis depend on early differentiation between those two infection types. Antibiotics are typically used to treat bacterial infections, though they are useless for treating viral infections and may even increase antibiotic resistance (Largman-Chalamish et al., 2022a). Different signalling pathways and recognition can be triggered by viral and bacterial infections. Bacteria are more likely to generate integrin-related gene expression profiles than viruses, which are more likely to trigger interferon (IFN)-related signatures. Bacterial infections are thought to be indicated by CRP, PCT, pro-ADM, CD64, CD55, IL-6, IL-8, CD35, whereas viral infections are thought to be indicated by CD46, IP-10, TRAIL, PTX3, MxA. These protein and RNA indicators originating from the host might all be utilised to distinguish between viral and bacterial illnesses. The most commonly used and suggestive biomarkers for detecting bacterial infections in children are CRP and PCT, as their levels are higher in bacterial infections than in viral ones. (Tsao et al., 2020).Its primary benefit over other acute phase reactants, such as CRP, ESR, and leukocyte count, is its specificity for bacterial infection. After a bacterial infection, the serum procalcitonin levels rise in 4–6 hours. Since it has a brief half-life of roughly 30 hours and is not metabolized in the plasma, it disappears rapidly after the initial injury is addressed ((Davies, 2015); (Vijayan et al., 2017b).In viral infections, serum procalcitonin is constant or even falls. Recent research has revealed a favourable correlation between the severity of COVID-19 and elevated procalcitonin levels (Hu et al., 2020). [Table 1]

Table1: Various Biomarkers involved in Bacterial infection and Viral infection

Biomarker	Bacterial infection indicators	Viral infection indicators	Specification	References
Protein	CRP, PCT, IL-6, IL-8, CD35, CD55, CD64	TRAIL, IP-10, CD46	CRP and PCT levels rise within 4-6 hrs for bacterial infection, but are low in viral infection; PCT is more specific	(Nakagawa et al., 2024b)
Gene	Integrin-related	Interferon (IFN) related	IFI27, RSAD2 for viral infection; integrin and MMP for bacterial infection	(Largman-Chalamish et al., 2022b)

3. Significatory role of PCT in different types of bacterial infections

Haemodialysis (HD) patients are more likely to get bacterial infections, which are linked to high rates of morbidity and death. Early diagnosis of such infections and prompt targeted antibiotic therapy are therefore crucial for reducing morbidity rates, lowering expenses, and improving patient condition because traditional laboratory markers to detect bacterial infections, such as erythrocyte sedimentation rate, white blood cell count and C-reactive protein (CRP) level, are frequently influenced by uraemia, extracorporeal treatment, or immunosuppressive medications (Tao et al., 2022). Blood culture-positive patients in this study had a higher prevalence of GN bloodstream infections (53.8% were GN bacteria, 31.9% were GP bacteria). According to earlier findings, Staphylococcus was the most prevalent GP bacteria and *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae* were the most prevalent GN bacteria. GN bacteria had a substantially greater median procalcitonin value than GP bacteria, albeit the exact process is unknown. Marshall et al. discovered that whereas GP bacteria do not raise TNF-a levels, GN bacteria do. Stronger inflammatory reactions may result from GN bacteria's induction of greater levels of IL-1, IL-6, and IL-10 than GP bacteria. These processes contribute to the explanation of why procalcitonin levels are higher in GN bloodstream infections than in GP ones (Lin et al., 2020).Patients with bacterial pneumonia have noticeably higher procalcitonin levels than those with tuberculosis (Abdullah Fikri et al., 2025b). As early as two to four hours after stimulation, this increase in procalcitonin levels can be seen, and it peaks six to twenty-four hours later. Because procalcitonin's concentration is unaffected by neutropenia, immunodeficiency conditions, and the administration of nonsteroidal or steroid anti-inflammatory medicines, it is thought to be the earliest and most stable sign, in contrast to C-reactive protein (CRP). (D. Liu et al., 2015a). It has been observed that MDR GN BSIs (Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*) have significantly higher PCT levels than non-MDR BSIs in hematological patients with febrile neutropenia. Additionally, we showed that PCT (best cutoff: 0.45 ng/mL) could distinguish between BSIs caused by MDR GN strains and non-MDR BSIs with a sensitivity of 72.6% and a specificity of 51.1%. Consequently, with a sensitivity of 55.2% and a specificity of 76.8%, the PCT cutoff value of(0.56 ng/mL) may be useful for forecasting BSIs brought on by a GN bacteria(Luo et al., 2019)

Among sepsis episodes, GN bloodstream infection was independently predicted by PCT level. It is in line with earlier findings that GN bloodstream infection had a noticeably higher PCT level than GP bloodstream infection and fungal bloodstream infection. The most frequent causes of sepsis are typically Gram negative rods and staphylococci belonging to the Enterobacteriaceae family. According to blood culture, patients with *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas* spp. had the highest PCT levels. Conversely, regardless of the severity of the disease, *Candida* spp., Streptococcus, and Enterococcus were linked to slightly higher PCT. Compared to GP infections, GN infections most likely produce more tumour necrosis factor alpha, and variations in interleukin plasma levels have also been observed. The higher PCT levels in GN bacteremia may be explained by the fact that GN bacteremia causes a stronger inflammatory response than GP bacteremia. Furthermore, PCT was lower than that of GN bacteremia but greater than that of bloodstream infection induced solely by fungal or negative bloodstream infection in cases of bloodstream infection caused by GN and *Candida* spp. (Zabawa et al., 2016) High rates of morbidity and mortality come from infections brought on by antibiotic-resistant microorganisms, especially GN bacteria, which pose serious therapeutic issues for doctors. Many substances that would normally be efficient antibacterial agents, including those that are effective against GP infections, are permeabilised by the outer membrane of GN bacteria. (Zabawa et al., 2016) An estimated 2.8 million antibiotic-resistant infections occur annually in the United States alone, making antibiotic resistance a rising global issue. These infections cause around 35,000 fatalities annually and are linked to higher rates of morbidity, mortality, and medical expenses. Drug-resistant GN bacteria are currently becoming more prevalent in the United States (Morris & Cerceo, 2020).

3.1 Impact of PCT on early screening of GNB infection

Early suitable medication in patients who actually have GNB (Gram Negative Bacterial) infections, a precise assessment of the patient's and hospital's risk of GNB infection is required before beginning an antimicrobial treatment. Reducing careless use lowers the incidence of fungal and *Clostridium difficile* infections and delays the selection of resistance.
(Bassetti et al., 2022)

From J.P Bedos et al it is observed that a sharp rise in antibiotic resistance has emerged as a serious public health concern linked to rising infection-related problems, a significant amount of excess mortality, and high healthcare expenses. Specifically, carbapenem resistance in GN bacteria is becoming more commonplace globally and leads to a variety of infections that are often very difficult to treat because carbapenem-resistant organisms are frequently also extensively drug-resistant (XDR; non-susceptibility to agents in all but two or fewer antibiotic classes) or multidrug-resistant (MDR; acquired non-susceptibility to agents in three or more antibiotic classes). According to the statement of the WHO in 2017, the development of novel antibiotics that are specifically effective against MDR and XDR GN bacteria should be the main goal of future research and development initiatives (Bedos et al., 2021). Since procalcitonin, C-reactive protein (CRP), is not impacted by immunodeficiency disorders, neutropenia, or the use of nonsteroidal or steroid anti-inflammatory medications, it is thought to be the most stable and early sign (D. Liu et al., 2015b). In hospitals and other institutional settings, serum procalcitonin levels are used to assess the prognosis of systemic bacterial infections, identify sepsis early, and identify secondary infections following surgery, severe burns, or trauma. Since other acute phase reactants rise in both bacterial and viral infections, the PCT level can also be utilized to determine the severity of sepsis and distinguish between the two in outpatient settings. It is notably useful for directing the prescription of antibiotics for respiratory tract infections. Additionally, it can identify renal involvement in UTI, meningitis, and pyrexia of unknown cause, as well as distinguish cellulitis from acute gout. According to various studies, Neonates with meningitis, sepsis, and UTIs have considerably higher blood PCT concentrations and the effectiveness of PCT in treating newborn infections has been validated by recent studies. As per the study findings, PCT's sensitivity and specificity were 76.9% and 100%, respectively, and its positive and negative prediction rates were 100% and 78%, respectively. Other significant applications include timely commencement and termination of antibiotic treatment, which lowers antibiotic use and the development of antibiotic resistance, and monitoring of sepsis patients' response to antibiotic therapy. From Ahmed et al, it is observed that PCT has prognostic utility in COVID-19 cases. ProCT and high-sensitivity CRP (hs-CRP) values are used to evaluate sepsis and septic shock in elderly patients in the intensive care unit. They found that ProCT and hs-CRP were helpful markers for the identification of sepsis and septic shock in patients older than 85 (Garnacho-Montero et al., 2014).

From Basma Bukhari et al it is shown that sepsis, especially when GN bacteria are present, can lead to severe organ failure and even death. The host inflammatory cascade is triggered by the production of acute-phase reactants and proinflammatory cytokines by GN bacteria. These inflammatory mediators, including TNFα, interleukin-1, interleukin-6, interleukin-8, and interleukin-10, are produced in greater quantities by GN bacteria. Researchers note that serum levels of procalcitonin (PCT) have also shown a similar increase (Bukhari et al., 2024). Since procalcitonin (PCT) is more specific for bacterial infections than either C-reactive protein (CRP) or white blood cell count (WBC), it has attracted a lot of attention. In addition to tracking infections, PCT has an excellent prognostic and kinetic profile, which makes it helpful for evaluating therapy response (Schuetz, 2023). (Table2)

Table2: Importance of PCT for GN bacterial infections compared with other biomarkers

Name of the biomarker	The Diagnostic Significance of GN bacterial Infection	Important Insights	References
PCT	Unique biomarker for bacterial infections, especially bacteraemia that is caused Gram-negative	When compared to GP bacterial infections (~0.48 ng/mL), PCT levels are substantially greater in GN bacterial sepsis (~7.47 ng/mL).	(Tao et al., 2022)
CRP	An indicator of general inflammation	CRP is less accurate in diagnosing bacterial infections than PCT and rises in numerous inflammatory diseases.	(Yang et al., 2014)
WBC	Regular hematological marker of infection	Although WBC increase is common in infections, it is not an accurate means to distinguish between Gram-positive and Gram-negative bacterial infections.	(Maegele, 2014)
IL-6	Early released of inflammatory cytokines following an infection	IL-6 increases quickly after infection, although it is not specific to bacterial infections and frequently has to be combined with other indicators.	(Schuetz, 2023)

3.2 Utility of PCT values in Gram Negative Bacterial Infection:

PCT is produced in response to bacterial endotoxins and inflammatory cytokines from the host, and may assist in differentiating between bacterial and viral infections, as well as distinguishing true bacteremia from contaminated blood cultures. It is understood that GP and GN bacteria, as well as fungi, trigger distinct Toll-like receptor (TLR) signalling pathways. This activation leads to the production of various pro-inflammatory cytokines, which in turn promote the release of PCT. This matter may be especially significant in cases of bloodstream infections, as PCT could help healthcare providers determine the most effective early treatment strategy, which is crucial for patient outcomes. Inappropriate initial antimicrobial treatment is an independent risk factor for poor outcomes in patients with bloodstream infections caused by *Staphylococcus aureus* or GN bacteria Leli et al., 2015b.When bacteremia is present, PCT is a quick and affordable biomarker that can reveal information about the pathogen group causing the illness. Additionally, patients with GN bacteremia have considerably higher PCT, indicating that PCT can be utilized to differentiate between GN sepsis and GP sepsis.(DOI: 10.5281/zenodo.14032461). The ProCT level can be used to distinguish between non-specific inflammation and bacterial infections. According to recent guidelines and research, ProCT-based antibiotic administration will reduce excessive antibiotic use and associated side effects, and tracking the ProCT concentration can be used as a prognostic factor to guide antimicrobial therapy. (Rojas-Moreno C, Regunath H. Procalcitonin in Sepsis.) Journal of Academic Hospital Medicine 2016;8.; Branche A, Neeser O, Mueller B, Schuetz P. Procalcitonin to guide antibiotic decision making. Curr Opin Infect Dis 2019;32:130–5.; Nunnally ME, Patel A. Sepsis - What's new in 2019? Curr Opin Anaesthesiol 2019;32:163–8.)

4 Emerging Advances in Procalcitonin-Based Diagnostics

4.1 Diagnostic Accuracy in Mixed Infections

There is a good chance that a diagnostic marker that provides information about the likelihood of bacterial infection and the resolution of the condition will enhance clinical evaluation of patients, help physicians make better antibiotic decisions, and maybe improve clinical outcomes. Recently, procalcitonin (PCT) has drawn a lot of attention as a supplement to clinical judgment. When epithelial cells come into contact with bacterial pathogens, PCT expression is elevated, which informs the first patient assessment about the danger of bacterial infection. Using a biomarker such as PCT its make a treatment decisions (Schuetz et al., 2019). PCT, a precursor peptide of calcitonin, is released by parenchymal cells as part of the innate immune mechanism's pro-inflammatory response and can potentially be detected four hours after endotoxin stimulation—much earlier than CRP. In CAP, a high PCT (often >2 ng/mL) appears to be a reliable indicator of a blood culture-positive pneumococcal infection. Amoxicillin treatment typically results in a quick drop in PCT, and the reason why high PCT levels persist is typically because of a pneumococcal pleural focus that medicines are unable to reach. In both adult and neonatal intensive care patients, PCT appears to be a helpful indicator for lowering the use of antibiotics.PCT seems to be a useful measure for reducing antibiotic use in both adult and neonatal intensive care patients. (Baumann et al., 2017). Accurate and timely diagnosis of bacterial infections, particularly bacteriuria, is crucial for patient outcomes in the ICU, as it can lead to serious infections (Zhang & Guo, 2024). Blood indicators of inflammation, such as procalcitonin (PCT) levels, have been demonstrated to aid in the diagnosis and surveillance of bacterial respiratory tract infections and urinary tract infections (UTI)(Mattoo & Spencer, 2024). According to certain research, PCT might not be an appropriate method for identifying UTIs (Sun et al., 2024).

4.2 Advancement in PCT- Based diagnosis

The most recent advancements in label-free biosensor technology combine cost-effectiveness, simplicity, ease of use, efficiency, accuracy, and quick detection of particular chemical markers with the encouraging trend of wearable platform development. For rapid PCT screening to identify sepsis, a small volume, high-sensitivity, and selective biosensor is being developed. The designed biosensor can be used as a sepsis screening tool for prognosis monitoring since it uses the semiconductor active sensing electrode to detect dual markers simultaneously. In addition, compared to previously published studies, the developed system needs the smallest sample size for best results (Tanak et al., 2019).

Instead of being a diagnostic marker, PCT should be viewed as a prognostic one that can reassure doctors that in some cases, extended treatment is not likely to be required. When employing a PCT cut-off value of <0.25 mg/L for noncritically ill patients with suspected or confirmed respiratory tract infections or <0.5 mg/L or 80% decline for critically ill patients with suspected or confirmed sepsis, there is strong evidence that the length of inpatient AMT can be safely and successfully shortened using PCT-guided algorithms (Scott & Deresinski, 2023).

5. Conclusion and Future Directions

Future research urges validating optimal procalcitonin cut-off values for gram-negative bacteremia across diverse clinical settings, including emergency departments, intensive care units, and immunocompromised populations. In the view of regulatory-aligned programmes frame PCT could be a measurable biomarker thereby reducing antibiotic susceptibility and hospital-acquired resistance. Furthermore, the recent AI era could offer amalgamation of PCT into clinical decision support algorithms combined with machine-learning models that incorporate demographic, microbiological, and other biomarker data, which may further tune diagnostic precision and demote unnecessary broad-spectrum antibiotic exposure in clinical settings. Additionally, cost-effectiveness analyses and implementation studies are noteworthy to screen PCT guided protocols influence on antimicrobial practices. This ultimately reduces the hospital stay and combat with resistance pathogenesis in gram-negative infection. With more accurate threshold definitions, optimized serial diagnostics protocols, via integration with standardized clinical pathways, PCT-guided assessment tools could intrinsically tailor the management of gram-negative bloodstream infections, ameliorating both diagnostic accuracy and early intervention strategies for good clinical outcomes.

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Conflict of Interest

The authors declared no conflict of interest

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