Procalcitonin As a Biomarker and Mediator of Sepsis: Implications for Critical Care

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Abstract

Sepsis represents the most common cause of death in noncardiac intensive care units (ICU). Procalcitonin (PCT), a peptide overexpressed ubiquitously during systemic inflammation, is considered the most sensitive and specific biomarker for bacterial sepsis. In this chapter, we provide an overview of the existing literature regarding the pathophysiology of PCT secretion, its diagnostic and

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prognostic accuracy, as well as its value in antibiotic stewardship. The impact of monitoring PCT levels in critically ill patients with COVID-19 infections is described. Finally, biologic functions of PCT and a potential mediator role in sepsis-related events are discussed. The use of PCT as a sepsis biomarker is a valuable aid for ICU physicians and may potentially improve the outcome of affected patients if interpretation of PCT measurements is performed adequately.

Keywords

Sepsis · Procalcitonin · Critical care · Biomarker · Infection · Antibiotic stewardship · COVID-19 · Immune system · Prognosis · *CALCA* gene

Abbreviations

ALA-PRO	Alanin-Proline
ARDS	Acute Respiratory Distress Syndrome
CALCA	Calcitonin-Related Polypeptide Alpha
CD11b	Integrin Alpha M
CGRP	Calcitonin Gene-Related Peptide
CGRP1	Calcitonin Gene-Related Peptide 1
CRP	C-Reactive Protein
CT	Calcitonin
CTR	Calcitonin Receptor
DDP IV	Dipeptidyl peptidase IV
E. Coli	Escherichia Coli
IgG	Immunoglobin G
IL	Interleukin
KO	Knockout
LPS	Lipopolysaccharide
MODS	Multiple Organ Dysfunction
N-PCT	N-Procalcitonin
PBMCs	Peripheral Blood Mononuclear Cells
PCT	Procalcitonin
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment Score
qSOFA	quickSOFA
TNFa	Tumor Necrosis Factor alpha

Introduction

Sepsis is a life-threatening complication of infection. Although most data are collected in high-income countries, sepsis is accountable for nearly 20% of all deaths worldwide (Rudd et al. 2020; Fleischmann-Struzek et al. 2020). As a result, the World Health Organization made sepsis a global health priority and adopted a resolution to improve the prevention, diagnosis, and management of sepsis

(*WHA70.7*). Over the past several decades, a substantial amount of research and improved clinical processes have increased the speed of recognition and treatment of sepsis. In 2016, a new definition was adopted (Sepsis-3) to further refine this process, with an increased focus on recognizing organ dysfunction in the context of a dysregulated host response to infection (Shankar-Hari et al. 2016). Sepsis is now defined as the presence of an infection combined with an acute change of ≥ 2 points in SOFA score, which estimates the overall functioning of six major organs (Table 1). Septic shock is defined as a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities increase the overall risk of mortality.

Sepsis represents a heterogeneous condition in which numerous humoral and cellular systems are activated, with a subsequent release of various molecules that mediate the host's response to infection. Bacteremia is only observed in about 30–43% of patients with sepsis, depending on age, previous antibiotic treatment, and severity (Brun-Buisson et al. 1996; Bates et al. 1997; Flayhart et al. 2007; Girard and Ely 2007). Early clinical signs of sepsis, such as fever, tachycardia, or leukocytosis, are nonspecific and overlap with signs of systemic inflammatory response syndromes (SIRS) of noninfectious origin, especially in patients who have suffered from major trauma or major surgery. Other clinical signs including arterial hypotension, thrombocytopenia, or organ dysfunction often manifest too late to initiate life-saving treatment. Delayed diagnosis and treatment initiation prolongs length of hospitalization, increases mortality, and the overall socioeconomic burden of sepsis. As clinical signs carry the potential risk of misinterpretation, biomarkers are playing an increasingly important role for early and reliable detection of sepsis.

The early identification of patients at risk of developing infectious complications is critical to enable early and appropriate treatment of sepsis. It has been demonstrated that prompt management of sepsis significantly prevents multiple organ dysfunction (MOD), reduces mortality and improves clinical outcomes (Dellinger et al. 2013; Cecconi et al. 2018a). Hence, a quantifiable sepsis parameter that allows early diagnosis and warrants early and appropriate treatment would provide optimal patient care. Based on the heterogeneous nature of sepsis-related events, multiple studies have been carried out to identify such a parameter, which also enables the differentiation between focal bacterial infection, sepsis, and/or noninfectious SIRS. Although a broad array of potential bloodstream biomarkers was tested for their ability to diagnose bacterial sepsis and to correlate with disease severity and outcome, Procalcitonin (PCT) has shown the highest sensitivity and specificity among all candidates investigated to date.

Pathophysiology of PCT Secretion

For a biomarker to be both sensitive and specific, it must be secreted into the blood stream during specific cellular and molecular events characteristic to the respective condition. In the case of sepsis, these events assumedly are triggered by the presence of bacteria or some of their cellular components in the systemic circulation. Mechanistically, bacterial components, defined as "pathogen-associated molecular

Table 1 The (q)SOFA score

System Parameter Unit	Respiration PaO_2/ FiO2 mmHg	CNS GSC	Circulation MAP or Vasopressors mmHg or µg/kg/min	Liver Bilirubin mg/dl	Coagulation Thrombocytes $\times 10^3$/µl	Renal Creatinine mg/dl
0	≥ 400	15	≥ 70	< 1.2	≥ 150	< 1.2
1	< 400	13–14	< 70	1.2–1.9	< 150	1.2–1.9
2	< 300	10–12	Dopamin ≤ 5 or Dobutamine	2.0–5.9	< 100	2.0–3.4
3	< 200 + mechanical ventilation	6–9	Dopamin > 5 or Adrenaline ≤ 0.1 or Noradrenaline ≤ 0.1	6.0–11.9	< 50	3.5–4.9
4	< 100 + mechanical ventilation	< 6	Dopamin > 15 or Adrenaline > 0.1 or Noradrenaline > 0.1	> 12.0	< 20	> 5
qSOFA	RR ≥ 22/min	< 15	Systolic BP ≤ 100			

The (quick) sepsis-related organ failure assessment (SOFA) score, modified according to (Vincent et al. 1996; Cecconi et al. 2018b). *BP* blood pressure, GCS Glascow Coma Scale, *CNS* central nervous system, *MAP* mean arterial pressure, *RR* respiratory rate

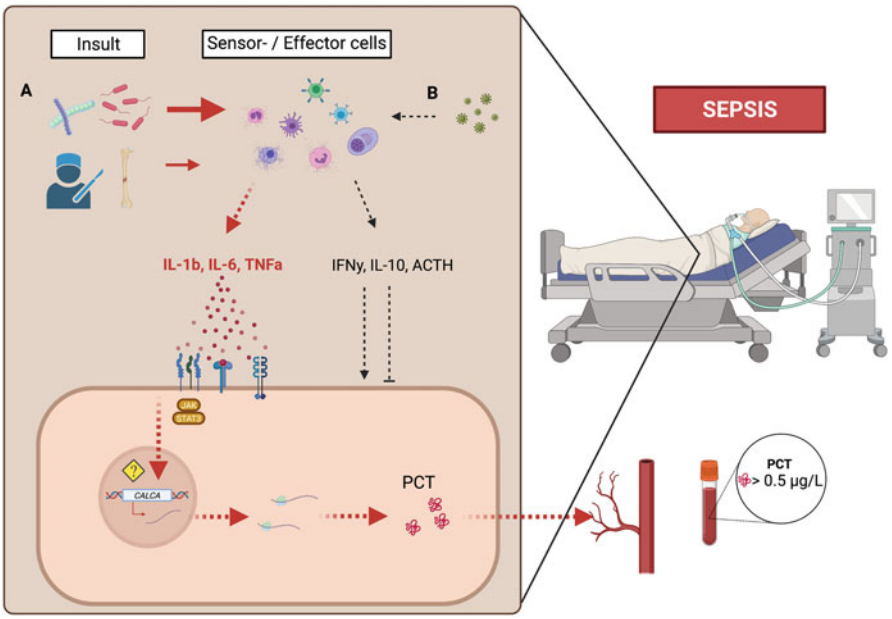

Fig. 1 Induction of PCT expression. **(A)** Bacterial infection, trauma, or major surgery may trigger immune responses, resulting in high concentration of specific circulating molecules and activated immune cells especially in the case of bacterial etiologies. By unknown mechanisms, these responses are associated with increased gene expression of *CALCA* ubiquitously, resulting in elevated PCT levels systemically. **(B)** Viral infections lead to altered levels of different sets of cytokines and chemokines with nonequivalent elevations of *PCT* levels. IL Interleukin, *TNFα* Tumor necrosis factor alpha, *IFNγ* Interferon gamma, PCT Procalcitonin.

patterns" (PAMP) including endotoxins or bacterial DNA, are recognized by the innate immune system through pattern-recognition receptors including toll-like receptors. This elicits an immediate immune response through activation of the intracellular core mediator nuclear factor κB, resulting in the release of numerous pro-inflammatory cytokines such as Interleukin-1, -6 (IL-1, IL-6), or tumor necrosis factor alpha (TNFa), among many others. Concurrently, anti-inflammatory molecules including IL-10, -11, -13, or hormones like adrenocorticotropic hormone (ACTH) raise in concentration to counteract the pro-inflammatory response (Opal and DePalo 2000; Cohen 2002) (Fig. 1). As a net result, the initially excessive pro-inflammatory state of the organism is shifted toward immune paralysis at later stages. On a functional level, the elevated concentrations of circulating inflammatory mediators result in vasodilation, increased vascular permeability, and reduced vascular resistance, leading to absolute volume depletion and hypoperfusion with ischemia in distant organs. Additionally, mitochondrial dysfunction may lead to impaired cellular oxygen utilization despite sufficient oxygen delivery, a phenomenon referred to as cytopathic hypoxia (Singer 2014). If the organism is unable to

counteract with compensatory increased cardiac output, cardiocirculatory failure occurs.

As high concentrations of calcitonin-like immunoreactivity have been reported in the blood of patients with various extrathyroidal diseases, Assicot et al. were the first to measure the calcitonin precursor PCT in patients with suspected infections. In their landmark publication in 1993, the authors demonstrated for the first time that high serum levels of PCT (6–53 µg/L) are found in patients with severe and invasive bacterial infection (Assicot et al. 1993), a finding which has been confirmed in countless clinical studies up to now. Structurally, the PCT peptide consists of 116 amino acids and is comprised of the amino terminus N-PCT, the calcitonin sequence, and the carboxy terminus sequence (Fig. 2). PCT is encoded by the *CALCA* gene, which through alternative splicing also gives rise to calcitonin gene-related peptide (CGRP), a neuropeptide known for its vasodilatory properties. While CGRP is synthesized in the central and peripheral nervous system in the healthy organism, PCT is primarily expressed in the thyroid gland and, after proteolytic cleavage, released as mature calcitonin into the circulation (Rosenfeld et al. 1983; Adema and Baas 1992). Although *CALCA* expression is comparatively strictly limited to thyroidal, neuronal, and neuroendocrine tissue, its expression becomes ubiquitous during sepsis and is detectable in nearly all tissues examined to date,

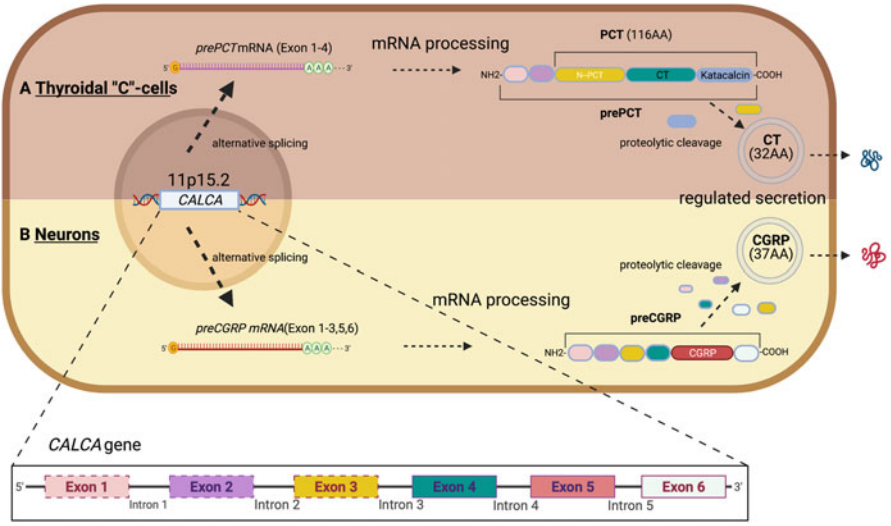

Fig. 2 Structure of the *CALCA* gene. **(a)** *CALCA* gene expression in thyroidal C-cells in the healthy organism. Once transcribed, PCT-mRNA strands are synthesized through alternative splicing. The PCT-mRNA is then translated into the PCT protein. After proteolytic cleavage of the N- and C-terminus, mature CT is stored in vesicles until release upon specific stimuli (e.g., serum calcium levels or other hormones). **(b)** In neurons, alternative splicing results in the synthesis of CGRP mRNA. After translation, CGRP protein is stored in vesicles and transported to nerve endings for release. *AA* Amino acid, *CT* calcitonin, *CGRP* Calcitonin-gene–related peptide, *CALCA* Calcitonin-related polypeptidealpha gene

including liver, lung, heart, muscle, fat, brain, and GI tract (Müller et al. 2001). Likewise, studies employing in situ hybridization showed that a broad array of different cell types within these tissues participate in the induction of *CALCA* expression (Linscheid et al. 2004). Although undetectable under normal conditions, considerate amounts of immunoreactive PCT are present in thyroidectomized individuals with sepsis (Silva et al. 1978).

Apart from PCT, the other *CALCA*-encoded peptide, CGRP, is also found at increased concentrations during sepsis. Based on its vasodilatory function, it was speculated that CGRP is involved in progressive hypotension during septic shock (Arnalich 1995; Arnalich et al. 1996; Beer et al. 2002; Shimizu et al. 2003). However, since the concentration of CGRP remains in the picomole range, it is not of great clinical value.

As global overexpression of a particular gene upon sepsis-related stimuli has not been reported for other peptides, this phenomenon seems to be unique for PCT. As noted by Becker at al. the entire organism functions as an endocrine gland during sepsis, secreting PCT in an ongoing and unregulated constitutive fashion (Burgess and Kelly 1987; Becker et al. 2010). It can be concluded that non-neuroendocrine tissue lacks the enzymatic potential to adequately process and activate the immature PCT peptide. It is currently not known why the calcitonin precursor protein is highly expressed in such pathologic settings, although it has been speculated that ubiquitous *CALCA* induction is mediated via stimulus-specific response elements within the promoter of the gene. Likewise, it is unclear why this mechanism has been evolutionarily conserved over a wide range of different species, and whether this phenomenon serves a particular purpose in the organism's response to invading bacteria or sepsis-related events.

To date, the key findings by Assicot et al. have been confirmed in hundreds of clinical studies, and serum PCT concentrations have been further correlated with severity of microbial invasion. PCT levels were shown to exhibit a short time of induction (within hours) after disease onset, a long half-life (approx. 24 h) and a wide biological range, with concentrations ranging from tens, to hundreds, to thousands of times the normal levels of less than 0.1 μg/L in bacterial sepsis (Meisner et al. 2001). In contrast, local bacterial, systemic viral and fungal infections are associated with only slightly increased PCT levels (0.1–1.5 μg/L) (Wacker et al. 2013). Additionally, PCT levels decrease rapidly upon appropriate antibiotic therapy (Cabral et al. 2018). Although a single biomarker is unlikely to provide a sufficiently comprehensive picture of sepsis progression, to date PCT is considered the most specific (55–94%) and sensitive (66–89%) biomarker for systemic bacterial infection (Müller et al. 2000; Tang et al. 2007; Hoeboer et al. 2015).

Diagnostic Accuracy

In the past several decades, substantial research has been conducted to precisely determine the diagnostic accuracy of PCT. However, heterogenic study approaches (sample timing, cut-off values, consideration of blood culture results) and alternating

definitions for sepsis have obscured a clear diagnostic significance. Therefore, it does not seem surprising that perspectives on PCT as a diagnostic and prognostic biomarker vary significantly among experts, and that PCT measurements have not been implicated in consensus guidelines for clinically suspected infection. As mentioned above, PCT was consistently found to be more specific in case of bacterial infections than any other commonly used inflammatory marker, including C-reactive protein, white blood cell count, or erythrocyte sedimentation rate. Importantly, the diagnostic accuracy of PCT was found to improve with worsening disease severity, demonstrating the highest accuracy (89% sensitivity and 94% specificity) in critically ill patients (Müller et al. 2000; Riedel et al. 2011; Wacker et al. 2013; Hoeboer et al. 2015). On the other hand, reported sensitivities ranging from 66% to 89% and specificities ranging from 55% to 79% illustrate the heterogeneity of clinical settings in which diagnostic accuracy was studied.

Observational studies showed that most patients with noninfectious SIRS have an inflammatory-mediated procalcitonin level between 0.3 μg/L and 0.8 μg/L, while patients with bacterial sepsis (from any source) in an ICU setting demonstrated levels ranging from 4.5 μg/L to 12.0 μg/L or higher (Castelli et al. 2004; Meynaar et al. 2011; Deng et al. 2013). In addition, rapid decline back to normal PCT levels most often indicated resolution of systemic inflammation. Therefore, the initial peak in PCT levels is regarded to reliably differentiate between bacterial sepsis and noninfectious SIRS in critically ill patients, which is not the case for alternative biomarkers including C-reactive protein (CRP) and IL-6. Furthermore, since the initial increase in serum levels usually precedes the onset of clinical symptoms, PCT allows an earlier detection of systemic infection compared to conventional standard methods.

The high prognostic value of PCT in sepsis was demonstrated in one large US study in which the kinetics of PCT levels within the first 72 h of ICU admission were strongly associated with mortality (Schuetz et al. 2017a). The authors concluded that mortality increases twofold if PCT levels do not drop by at least 80% from the initial maximum within this time frame, representing a significant independent predictor. Importantly, nonbacterial etiologies that moderately increase PCT include severe trauma, cardiac arrest, surgery, burns, pancreatitis, malaria, invasive *Candida* infections, or intracranial hemorrhage. However, in these settings PCT levels are consistently found to be significantly lower than in sepsis (Meisner et al. 1998; Charles et al. 2006; Deng et al. 2013; Engel et al. 2013; Bruneel et al. 2016; Cabral et al. 2018; He et al. 2018; Alrawahi et al. 2019; Shi et al. 2021) (Table 2).

Most studies investigating the diagnostic reliability of PCT in local infections relied on study cohorts with pulmonary infection, as pneumonia represents the most common site of infection leading to sepsis. The diagnostic accuracy of PCT (AUC=0.75) for pneumonia alone was found to be lower than IL-6 (AUC=0.80) or CRP (AUC=0.82) (Wussler et al. 2019), but it was still possible to distinguish pneumonia from a COPD exacerbation or asthma (Bafadhel et al. 2011). Interestingly, median procalcitonin levels were higher (2.5 μg/L) in patients with pneumonia caused by typical bacteria, such as *Streptococcus pneumoniae* or *Staphylococcus aureus,* compared to atypical bacteria (0.20 μg/L) or viruses (0.09 μg/L) (Self et al.

Table 2 PCT reference ranges in relevant clinical conditions

Infection	PCT range in μg/L	Citation
None	< 0.1	Assicot et al. (1993)
Local infection	0.1–1.5	Wacker et al. (2013)
Beginning sepsis	0.5–2.0	Vijayan at al. (2017)
Severe bacterial sepsis	6–53	Assicot et al. (1993)
Severe virai sepsis	0.05–0.54	Self et al. (2017)
Severe fungal sepsis	< 5.5	Charles et al. (2006)
Malaria	5.6–41.1	Bruneel et al. (2016)
Non-infectious SIRS	0.3–0.8	Castelli et al. (2004) and Meynaar et al. (2011)
Other causes	**PCT range in μg/L**	Citation
Minor/aseptic surgery	0.18–0.6	Meisner et al. (1998)
Major surgery	0.3–1.49	Meisner et al. (1998)
TBI	0.08–0.31	Deng et al. (2013)
Intracranial hemorrhage	0.035–0.078	He et al. (2018)
Burn > 15% of body surface	2.1–7.0	Cabral et al. (2018)
Cardiac arrest	1.08–3.07	Engel et al. (2013)

An overview of exemplary human PCT values related to infectious and non-infectious conditions. Overall, higher PCT levels can be observed in severe bacterial infection, while viral sepsis and noninfectious conditions increase PCT only slightly above the reference range

Table 3 PCT levels related to different pathogens

Pathogen	Mean PCT value in μg/L	Regression coefficient
S. aureus	7.2	0.00[1] (p = 0.1)
Streptococcus spp.	18.2	0.50 (p = <0.001)
Enterococcus spp.	6.8	0.06 (p = 0.6)
E. coli	26.8	0.50 (p = <0.001)
Other enterobacteriaceae	24.9	0.49 (p = <0.001)
P. aeruginosa	23	0.04[1] (p = 0.8)
Candida spp.	4.7	-

PCT values and regression coefficients associated with bacteremia of different pathogens. Modified after (Thomas-Rüddel et al. 2018) [1]values were calculated for Streptococcus spp. and Pseudomonas spp., respectively

2017). Among atypical bacteria, *Legionella* species were reported to cause only modest elevations in PCT, while *Mycoplasma* and *Chlamydia* species may not be associated with detectable elevations (Haeuptle et al. 2009; Bellmann-Weiler et al. 2010) (Table 3). Most importantly, PCT-guided antibiotic stewardship for pneumonia did not lead to improved outcomes (Huang et al. 2018). In other locally confined infections, such as urinary tract infections, PCT plays only a limited role in diagnosing or monitoring disease progression (van der Starre et al. 2014).

While PCT does not have a clinical use in diagnosing localized bacterial infections, it is useful for early diagnosis of sepsis and allows clinicians to estimate disease severity and outcome when measured on a regular basis. However, PCT levels must be interpreted carefully in the context of medical history, physical examination, and microbiological assessments.

Procalcitonin-Guided Antibiotic Stewardship

Besides early diagnosis, immediate and adequate antibiotic therapy is of vital importance in treating sepsis in critically ill patients. However, excessive and prolonged antimicrobial treatment is undesirable due to potential antibiotic resistance and damage to the physiological microbiological flora, harboring more than five trillion bacteria (Jernberg et al. 2010; Shin et al. 2015). Individualizing antibiotic treatment improves antibiotic stewardship efforts to encourage reasonable and indicated use of these agents, which mitigates the emergence of multidrug-resistant pathogens, one of the most imminent threats to global health directly linked to antibiotic overuse (WHO, 2020. Antimicrobial Resistance. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. Accessed: 30 Sep 2021). Therefore, specific markers for the resolution of infection may assist physicians in making adequate decisions regarding antibiotic therapy on a more personalized basis. However, physicians may be especially reluctant to shorten the duration of antimicrobial treatment in critically ill patients.

Much research has focused on the potential benefits of using serum PCT levels to guide antibiotic therapy (referred to as PCT-guided antibiotic stewardship), especially in patients suffering from proven or suspected bacterial infection in the ICU. As discussed above, PCT has been advocated as a biomarker with higher specificity and sensitivity than any other biomarker for monitoring the course of sepsis in critical ill patients. Mounting evidence indicates that PCT guidance is associated with a reduction in treatment duration and the daily antibiotic dose in critically ill patients with presumed bacterial infection, which may reduce overall mortality.

In this regard, Wirz et al. compared 2,252 PCT-guided ICU patients with 2,230 control group patients and found an earlier discontinuation of antibiotics with a reduction in treatment duration in PCT-guided patients (9.3 days vs 10.4 in control), with stronger reductions seen in patients with less severe sepsis and those with initial respiratory infections. This meta-analysis revealed that PCT use was found to result in significantly improved survival (21.1% mortality in PCT-guided vs 23.7% in control group, $p = 0.03$), which was consistent in subgroup analyses stratified by type of infection, Sepsis-3 definition, or severity of sepsis (Wirz et al. 2018). In contrast, in a randomized clinical trial, Bloos et al. found no significant differences in the frequency of diagnostic or therapeutic procedures, although there was still a reduction in overall antimicrobial exposure from 862 days in the conventional group to 823 days in the procalcitonin guidance group (4,5%, $p = 0.02$). However, the

recommendation to stop antimicrobial therapy, based on serial PCT measurements on day 0, 1, 4, 7, 10, and 14 after admission, was overruled by the treating physicians in 50.4% of cases due to the presence of fever, microbiologic findings, or changes in white blood cell count. In this study, PCT was measured only every 3 days, which could result in loss of potential antibiotic-free days (Bloos et al. 2016). In the PRORATA trial, daily PCT measurements in patients receiving antibiotics led to a decrease in treatment duration of nearly 3 days with no changes in overall mortality (Bouadma et al. 2010). Of note, this study included patients with less severe disease, which may have resulted in a more confident handling of antibiotic discontinuation. Similarly, a randomized, controlled, open label trial demonstrated reduced antibiotic exposure and mortality in the ICU when measuring PCT levels daily. In the PCT-guided group, the median consumption of antibiotics was 7.5 days versus 9.3 in the control group. Furthermore, mortality was found to be significantly higher in the control group (25% within 28 days and 43% after 1 year) than it was stated for the PCT-guided group (20% within 28 days and 36% after 1 year, $p=0.0122$). The advice to discontinue antibiotics was defined by 80% reduction of initial PCT levels or a level of 0.5μg/L or lower (de Jong et al. 2016). Additionally, a recently published meta-analysis demonstrated that patients with sepsis and confirmed bacteremia exhibit a lower antibiotic exposure by almost 3 days without an apparent increase in mortality when subjected to PCT-guided management (Meier et al. 2019). Infections with gram-positive bacteria or *Escherichia coli* tended to resolve with shorter antibiotic use compared to other bacteria.

In such complex settings, it remains unclear whether the reduction in antibiotic exposure fully explains the differences in mortality reported by some authors. Low adherence to PCT-guided algorithms was an issue in trials failing to demonstrate a benefit of PCT-guided care. Current evidence on other types of infections is sparse and few studies have included patients with immunosuppression, limiting the generalizability of respective conclusions to more vulnerable patient populations. Another important consideration is the quality of PCT assays, which varied considerably among the most important clinical studies discussed above. Only high-sensitivity PCT assays should be used in clinical practice on a daily basis, as semiquantitative assays may not detect changes in PCT levels at lower ranges. Since clinical judgment and monitoring of standard laboratory parameters plays an important role in most modern ICU settings, training and experience in the proper use of PCT is essential.

Overall, individualization of antibiotic treatment regiments based on biomarker levels is preferable to the use of rigid treatment regiments. As a marker with both diagnostic and prognostic implications, PCT-guided antibiotic stewardship has shown promising and consistent evidence in its ability to reduce antibiotic use and improve clinical outcomes in critically ill patients with sepsis, if measured daily. This could be an important step in promoting the judicious and correct use of antibiotics, and aid in mitigating the further evolution and spread of multidrug resistant pathogens (Fig. 3).

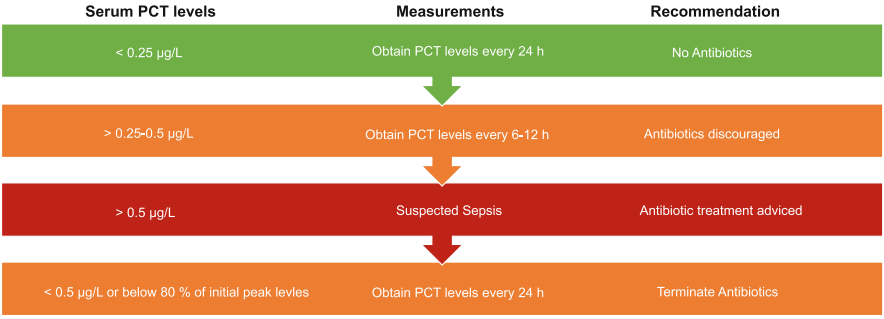

Fig. 3 PCT-guided treatment algorithm. Recommended schematic PCT-guided antibiotic stewardship. Initiation of empirical antibiotic treatment is recommended when PCT levels start to rise above 0.5 mg/L. Discontinuation of antibiotics is recommended when PCT serum levels drop below 80% of initial peak values or fall below 0.5 mg/L

COVID-19 and PCT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or coronavirus disease 2019 (COVID-19) is a pandemic disease, resulting in high intensive care burden. Prior to the introduction of vaccine against SARS-CoV-2, about 80% of cases experienced mild symptoms such as fatigue, dry cough, or fever and recovered without hospitalization. Around 14% required ventilation in an ICU setting, and 5% were classified critical, as they are associated with acute respiratory distress syndrome or respiratory failure, sepsis, acute cardiac injury, and heart failure (Yang et al. 2020).

COVID-19 infection is initiated by viral spike protein S1 attaching to its complementary host cell receptor (ACE2R), which is highly expressed in the respiratory tract, leading to endocytosis of the virus. The virus replicates and spreads in lytic cycles while the host's immune response is triggered to contain the pathogen, resulting in considerably high cytokine concentrations (Hu et al. 2021). Subsequently, the lung tissue is damaged and thus more susceptible to secondary bacterial infection, as seen in 3.2–14.3% of COVID-19 patients, adding to the mortality in severe cases (Chen et al. 2020; Hughes et al. 2020; Langford et al. 2020; Rawson et al. 2020b; Wu and McGoogan 2020; Garcia-Vidal et al. 2021).

Since PCT is a biomarker for bacterial infections, the initial levels usually remain unaltered during the admission of viral COVID-19 patients exhibiting mild symptoms (Zeng et al. 2020; Gao et al. 2021). General inflammation parameters such as leukocyte count and CRP are frequently elevated at the time of diagnosis, but do not allow differentiation between viral and bacterial infection. Evidence has shown that PCT levels increase significantly in critical or fatal COVID-19 courses (Chen et al. 2020; Guan et al. 2020; Huang et al. 2020; Rello et al. 2020; Zhang et al. 2020; Yan et al. 2020). Interestingly, initial elevated PCT values have been associated with a nearly fivefold higher risk of severe SARS-CoV-2 infection (Hu et al. 2020; Gao et al. 2021). Furthermore, between 25% and 36% of deceased patients had PCT

levels of 0.5 μg/L or higher, whereas only 2 % of patients recovered from such high levels (Guan et al. 2020; Zhou et al. 2020). This observation suggests that PCT levels in COVID-19 patients may be important in dynamically predicting disease severity and provide information about subsequently occurring secondary infections.

Most patients with COVID-19 receive antibiotics (79 %) but only 14.3 % exhibit secondary bacterial infection (Langford et al. 2020; Rawson et al. 2020a; Garcia-Vidal et al. 2021). The adverse events caused by unnecessary use of antibiotics could potentially be reduced, as this widespread use is not supported by contemporary data (Langford et al. 2020). Interestingly, 93 % of all deceased and 89 % of all recovered patients received empirical antibacterial therapy (moxifloxacin, cefoperazone, or azithromycin), which leads to the conclusion of no advantage in terms of survival after rigid antibiotic treatment (Chen et al. 2020). Moreover, use of broad-spectrum empiric antibiotics were associated with higher mortality (Rhee et al. 2020). Although larger studies are needed, a prospective, single-center, cohort study suggests that the use of PCT as a guide for de-escalation of antibiotics significantly reduced antibiotic usage by 2 days in COVID-19 patients (Heesom et al. 2020).

Overall, currently available data show that serum levels of PCT increase significantly as COVID-19 disease deteriorates. Therefore, daily measurement of PCT levels may be important for the decision on whether additional antibiotics are indicated in severe and critical cases of COVID-19 infection.

Experimental Data on a Potential Mediator Role of PCT

Even though PCT represents a valuable biomarker in sepsis and sepsis-related events, it is unclear why the calcitonin precursor protein is highly expressed ubiquitously in such pathologic settings, and why this mechanism has been evolutionarily conserved over a wide range of species. While the biologic function of other biomarkers, for example, TNFα or IL-6, have been studied intensively, only limited information regarding a potential mediator role of PCT is available. Possible reasons include the limited availability of adequate gene deficiency models due the complex organization of the *CALCA* gene (Hoff et al. 2002). Furthermore, PCT levels are barely measurable in the healthy organism, contributing to the ongoing challenge to understand its function. Thus, a clearly defined role of PCT in health and disease is still missing. However, as PCT expression is increased in most vertebrates during sepsis (Redl et al. 2001; Bonelli et al. 2015; Perez-Ecija et al. 2021), experimental approaches employing laboratory animals and cell culture systems have brought forward our understanding of PCT action during systemic inflammation to some extent, as discussed in the following sections.

PCT Mediates Cytokine Release and Immune Cell Migration

Whereas thyroidal C cells are the principal source of the minute amounts of circulating PCT under physiological conditions, large quantities of PCT are released

from various peripheral tissues in sepsis. In hamsters with an experimentally induced, systemic *E. Coli* infection, PCT levels in the spleen, liver, adrenal glands, brain, and spine increased hundreds-fold over controls and reached more than tenfold over controls in six distinct major organs including lung, pancreas, and kidney (Müller et al. 2001). Moreover, in vitro experiments using a variety of different cell types showed that different pro-inflammatory signals are capable of inducing *CALCA* expression. For example, liver samples from healthy donors were found to produce PCT upon stimulation with TNFα or IL-6, even without addition of lipopolysaccharide (LPS) (Nijsten et al. 2000). In a different study, human peripheral mononuclear blood cells, in particular lymphocytes and monocytes, were shown to release PCT upon incubation with LPS only (Oberhoffer et al. 1999). In addition, Linscheid et al. reported a transient overexpression of *CALCA* mRNA in human monocytes after incubation with IL-1β and LPS, which eventually returned to baseline after 18 h (Linscheid et al. 2004). However, anti-inflammatory molecules such as IL-10 did not affect PCT expression in human mononuclear cells (Oberhoffer et al. 1999). Incubation of renal mesangial cells with PCT alone led to a time-dependent increase in IL-6 and TNFα (Araujo et al. 2013), pointing toward a feed-forward mechanism between bacterial stimuli and inflammatory signaling. In a different study, reduced levels of anti- and proinflammatory signals after pre-incubation of human PBMCs with PCT have been reported (Matera et al. 2012). These contrasting results might indicate a more complex regulation in a time-dependent manner in vivo, even though the exact same concentrations of PCT have been employed in the respective studies in vitro. In clinical trials, PCT reached its peak later than other inflammatory markers (Bloos 2015) and studies investigating the effects of preincubation with PCT should therefore be carefully interpreted.

From a functional perspective, evidence for pro-inflammatory effects of PCT has been found in different in vitro studies, where aberrant immune cell migration and endothelial function under incubation with PCT was observed. In particular, PCT inhibited LPS-induced expression of factor CD11b on neutrophiles and macrophages in a dose-dependent manner, thus decreasing the migration of immune cells toward the site of infection and presumably augmenting levels of inflammatory immune cells in the bloodstream (Monneret et al. 2003). Furthermore, PCT increased the intracellular calcium uptake of monocytes and neutrophiles derived from human whole blood samples with the same efficiency compared to LPS (Wei et al. 2008), substantiating further evidence on potential pro-inflammatory properties of PCT. In addition, PCT deactivated chemotaxis of monocytes and neutrophils in the presence of other chemotactic factors in different trials (Wiedermann et al. 2002; Liappis et al. 2011). However, no direct interference or toxic effect on bacteria has been observed to date, supporting the hypothesis that PCT acts as a crucial mediator of sepsis with a function similar to acute phase proteins and immunomodulatory cytokines.

In contrast to the above considerations, two different studies reported anti-inflammatory effects of PCT and raised further speculation about a beneficial and thus evolutionarily conserved role of PCT. First, addition of exogenous PCT to a

whole-blood culture model incubated with LPS diminished TNFα levels by up to 27 %, even though the applied dose of PCT (10^{-7} M) exceed pathophysiological PCT levels in sepsis, and results should therefore be subject to careful interpretation (Monneret et al. 2000). Second, PCT inhibited TNFα-dependent overexpression of inducible nitric oxide synthase in rat vascular muscle cells (Hoffmann et al. 2001), potentially representing compensatory mechanism for hypotension in patients with septic shock. In contrast, Wagner et al. reported PCT decreased vascular endothelial cadherin expression, and therefore disrupted the endothelial barrier, contributing to the capillary leakage clinically observed in sepsis (Wagner et al. 2017).

Neutralization of PCT Is Associated with Reduced Mortality and Morbidity in Experimental Sepsis

As most in vitro studies described above reported divergent functions of PCT and do not allow definite conclusions regarding its functions, a considerate amount of experimental in vivo studies have also been conducted. Human PCT levels rise multifold during sepsis, and a similar response has been observed in other vertebrates. A prospective study found PCT levels of septic horses to be increased 10-fold in comparison to baseline in healthy controls (Bonelli et al. 2015). In addition, experimental sepsis caused by injection of LPS or lethal total body irradiation raised levels of PCT in dogs up to 2.5-fold and in rodents up to 20-fold, respectively (Biju et al. 2012; Easley et al. 2020). In baboons, a similar PCT response toward an infusion of *E. Coli* was observed, and excessive levels of PCT were measured in lethal courses of disease (Redl et al. 2000).

Concurrently, trials investigating the effects of exogenous PCT administration as well as PCT blockage in experimental sepsis have been carried out (Fig. 4). Over two decades ago, Nylen et al. reported an increase in lethality from 43% to 94% after treating septic hamsters with human PCT. Within the same study, blockage of PCT via immunoreactive goat serum decreased rodent mortality by 50 % (Nylen et al. 1998). In a large animal study, rabbit serum with IgG targeting the aminoterminus of PCT was administered to pigs 3 hours after induction of sepsis and led to improved cardiac and renal function, as well as increased short-term survival (Martinez et al. 2001). Under the same experimental conditions, administration of PCT-reactive rabbit serum during the induction of sepsis had similar positive effects on porcine cardiac index, creatinine clearance, and short-term survival (Wagner et al. 2002), giving further evidence for a crucial role of PCT during early stages of infection. From a structural point of view, it is yet to be determined whether the ALA-PRO sequence, hence N-PCT, is responsible for the observed pro-inflammatory effects of PCT. Two distinct trials reported improved outcomes in sepsis after neutralization of N-PCT. In particular, septic rats displayed an inhibition of inflammatory cytokine production, as well as increased survival rates upon treatment with a highly specific N-PCT antibody (Tavares and Miñano 2010). Furthermore, the severity of acute lung injury following sepsis was significantly reduced by administration of anti-rat N-PCT after induction of sepis (Tavares et al. 2014).

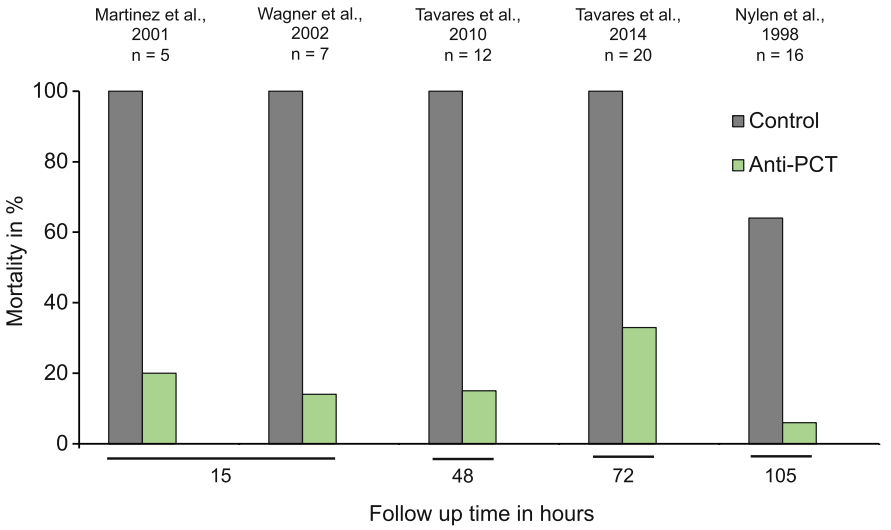

Fig. 4 PCT antibodies in experimental sepsis. Treatment with antibodies neutralizing PCT improves survival in various animal models of experimental sepsis within observation periods ranging from 15 up to 102 h

The role of mice as an adequate model to investigate PCT in sepsis has been critically examined, as a study employing models of severe bacterial infection did not observe extrathyroidal PCT expression or release in WT, nor a difference in survival in *CALCA*-deficient mice, despite the fact that exposure to respective bacteria in the respiratory tract or in the abdomen provoked lethal courses in 20–80% of all cases (Tuvim et al. 2013). In contrast, using more aggressive models of experimental sepsis including LPS injection and cecal ligation and puncture with mortality rates of 100%, Baranowsky et al. detected increased *CALCA* expression and elevated PCT levels in septic mice, even though the respective increases were rather small compared to humans with sepsis (Baranowsky et al. 2021). In these models, mice lacking *CALCA* demonstrated a moderate, yet significant survival benefit, indicating that overall PCT exerts a negative effect on disease outcomes in sepsis. Mechanistically, an immunomodulatory effect of PCT on innate immune cells including macrophages was observed, resulting in increased release of pro-inflammatory IL-17a from gamma delta (γδ) T cells (Baranowsky et al. 2021).

Limited information is available to date on the relevant PCT receptor. Sexton et al. investigated whether PCT has bioactivity at the calcitonin receptor family complexes. The authors showed that PCT had only moderate activity at the calcitonin receptor (CTR) but acted as a partial agonist at the calcitonin receptor-like receptor (CGRP receptor) in vitro (Sexton et al. 2008). In this regard, Baranowsky et al. found that mice lacking CTR globally did not display altered

survival curves during sepsis, ruling out CTR as the biologically relevant PCT receptor in vivo. However, application of the CGRP receptor antagonist olcegepant, initially developed for the treatment of migraine, resulted in improved survival in experimental sepsis in a PCT-dependent manner. Together, these results indicate that the harmful effects of PCT observed in experimental sepsis are mediated by the CGRP receptor, at least in mice (Baranowsky et al. 2021). However, blockage of the CGRP receptor did not improve survival in a porcine model of autologous polymicrobial sepsis, suggesting that therapeutic usage might be limited due to adverse effects on the cardiovascular system (Messerer et al. 2022).

In sum, experimental research provides comparatively strong evidence for a mediator role of PCT in sepsis. Beneficial effects of PCT-neutralization or CGRP receptor antagonism in different experimental settings (Nylen et al. 1998; Tavares et al. 2014; Baranowsky et al. 2021) further suggest PCT as a potential pharmacologic target to improve disease outcomes in patients with sepsis.

Applications to Prognosis

As a biomarker with both diagnostic and prognostic use in clinical practice (Riedel et al. 2011; Wacker et al. 2013; Hoeboer et al. 2015), stringent PCT-guided antibiotic stewardship consistently reduced antibiotic use and improved outcomes in critically ill patients with sepsis, if measured daily. The current recommendation to discontinue antibiotics was defined by an 80% reduction of initial PCT levels, or a serum concentration of 0.5 μg/L or lower (de Jong et al. 2016; Schuetz et al. 2017b). Since multidrug-resistant pathogens represent an increasing threat to global health (WHO, 2020 Antimicrobial Resistance https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. Accessed: 30 Sep 2021), the use of individualized antibiotic treatment regimens guided by one or more biomarkers is considered advantageous over rigid treatment regiments.

Applications to Other Diseases or Conditions

Although a biomarker role of PCT was first reported in a pediatric population with sepsis (Assicot et al. 1993), most clinical studies investigated PCT in adults only. Concerning neonatal sepsis, a condition primarily affecting infants, which were delivered preterm and/or with a low birth weight, PCT was found to have a higher sensitivity and specificity for diagnosing early-onset (<72 h after birth) sepsis when compared to IL-6 and CRP, respectively (Chiesa et al. 2003). More recently, PCT was found to be superior for estimating outcome of late-onset (>72 h after birth) neonatal sepsis in comparison to CRP and correlated with 7-day mortality in a similar manner as IL-6 (Kurul et al. 2021). Overall, PCT might be a valuable diagnostic and prognostic biomarker independent of age.

Mini-Dictionary of Terms

- **Antibiotic Stewardship.** Rational and responsible use of antibiotics through the detection of a (bacterial) infection, the choice of appropriate antibiotic, adaptation of duration of therapy, dosage, and form of antibiotic administration.
- **C-reactive Protein.** An acute phase protein of hepatic origin. Clinically used as a biomarker to estimate the severity of overall infection.
- **Interleukin-6.** A pro-inflammatory cytokine which is, upon infectious stimuli, derived from various cells such as macrophages, monocytes, and endothelial cells.
- **Procalcitonin.** A 116-amino acid bioactive molecule, which is encoded by the *CALCA* gene. It is found to play a mediator role in sepsis and is clinically used to diagnose systemic bacterial infection.
- **Sepsis.** Severe organ dysfunction upon an infectious stimulus with increased risk of overall mortality.
- **Systemic inflammatory response syndrome.** Severe organ dysfunction due to a systemic inflammatory response to noninfectious stimuli.

Key Facts of Procalcitonin As a Biomarker and Mediator of Sepsis: Implications for Critical Care

Key Facts of PCT As Prognostic Marker of Sepsis

Patients with severe or systemic bacterial infections display significantly increased PCT values. Diagnosis of sepsis should be based on clinical features (e.g., qSOFA score) in combination with biomarkers (e.g., PCT, IL-6). Measuring PCT on a regular basis may help to predict severity and outcome of sepsis. In addition, rapidly decreasing PCT values can be used as a guide for discontinuation of antibiotic treatment.

Key Facts of PCT in COVID-19

In COVID-19 patients with mild symptoms, PCT levels are usually within the physiological reference range upon admission. In critically ill patients or lethal courses of the disease, PCT increases significantly. In addition, 14.3% of COVID-19 patients suffer from secondary bacterial infection. PCT therefore may be used to predict the clinical course and outcome of COVID-19 infections. Interactions of empirical antibiotic usage and potential adverse effects must be taken into consideration.

Key Facts of PCT in Experimental Sepsis

Most vertebrates display increased PCT levels in severe bacterial infection and sepsis. The addition of exogenous PCT increases mortality in experimental sepsis. In turn, antibodies against PCT improve survival in experimental sepsis in pigs, hamsters, rats, and mice. Harmful effects of PCT might result from its action on the CGRP receptor.

Summary Points (5–15)

- Sepsis accounts for nearly 20% of deaths worldwide, while bacteremia is only observed in 30–40% of patients.
- In sepsis, PCT is released ubiquitously from nearly all tissues and serum levels can rise hundreds-fold above the reference range (< 0.1 μg/L).
- PCT is the biomarker with the highest sensitivity and specificity for diagnosing bacterial sepsis.
- Higher levels of PCT are associated with higher risk of severe SARS-CoV-2 infection.
- Inhibition of PCT or its receptor decreases mortality in experimental sepsis.

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