# Procalcitonin in bacterial infections – hype, hope, more or less?

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## Summary

An ideal marker for bacterial infections should allow an early diagnosis, inform about the course and prognosis of the disease and facilitate therapeutic decisions. Procalcitonin (ProCT) covers these features better as compared to other, more commonly used biomarkers, and thus, the current *hype* on ProCT has a solid scientific basis. A superior diagnostic accuracy of ProCT has been shown for a variety of infections, eg respiratory tract infections, meningitis, acute infectious endocarditis and pancreatitis. Importantly, a ProCT-based therapeutic strategy can safely and markedly reduce antibiotic usage in lower respiratory tract infections, the major cause of sepsis. Being a hormokine mediator, immunoneutralisation of ProCT might offer new *hope* for more effective treatment options in sepsis. It is now evidence-based that ProCT provides *more* information and, thereby, questions the currently used "gold standards" for the diagnosis of clinically relevant bacterial infections. Yet, ProCT is *less* than a perfect marker. ProCT can be increased in non-infectious conditions, and may remain low in infections. The diagnosis of bacterial infections will continue to require a critical clinical awareness, careful patient history, dedicated physical examination, and appropriate cultures. This review aims to help the clinician to understand the physiopathological basis, to appreciate strengths and weaknesses of this biomarker, and thereby to promote a rational implementation of ProCT in a routine setting.

*Key words: infection; procalcitonin; diagnosis; sepsis*

## What is procalcitonin?

Procalcitonin (ProCT) is a precursor peptide from the hormone calcitonin (CT) [1] (figure 1). After translation from CT-messenger RNA (mRNA), ProCT is cleaved enzymatically into smaller peptides, finally to yield the thirty-two amino acid mature CT [2]. Most CT precursor peptides, including ProCT, are found in the serum of normal persons.

Mature calcitonin (CT), named after its mild and transient hypocalcaemic effect, was originally thought to be a hormone exclusively of thyroidal C-cell origin and to play an important role in skeletal homeostasis [3, 4]. However, provided that thyroid hormone is replaced, thyroidectomy in humans has no important pathologic consequences: calcium homeostasis remains intact and bone density is not decreased [5, 6]. Possibly, different CT peptides (eg, CT, CT gene related peptide [CGRP]) had once an evolutionary role in becoming vestigial in the context of establishing, protecting and regulating the skeletal mass [7]. However, the presence of the parathyroid gland and other evolutionary changes occurring in tetrapods suggest that the function of the mature CT hormone in humans is no longer essential [8].

Conversely, in microbial infections and in various forms of inflammation, circulating levels of several calcitonin precursors, including ProCT but not mature CT, increase up to several thousand-fold. This increase and especially the course correlates with the severity of the condition and with mortality [9–12].

## ProCT – the molecular basis for the increase in inflammation and infection

In the traditional endocrine view, mature CT is produced mostly in neuro-endocrine C-cells of the thyroid. In the absence of infection, the extra-thyroidal transcription of the CALC-I gene is suppressed and is restricted to a selective expression in neuro-endocrine cells found mainly in the thyroid and lung. In these neuroendocrine cells, the mature hormone is processed and stored in secretory granules [4, 13].

Interestingly, a microbial infection induces an ubiquitous increase of CALC-I gene-expression and a constitutive release of ProCT from all parenchymal tissues and differentiated cell types throughout the body [14] (figure 2). Thus, under

**Figure 1**

Schematic illustration of human procalcitonin. Procalcitonin and its constituent peptides, which are found in the free form in normal human serum. Initially, procalcitonin consisting of 116 aminoacids is secreted. Due to rapid cleavage by dipeptidases, 114 aminoacid long procalcitonin is found in the circulation. Additional cleaving leads to circulating aminoprocalcitonin, immature calcitonin and calcitonin carboxypeptide-I (CCP-I), previously known as katacalcin. In sepsis, these peptides are variably increased, often to huge levels due to ubiquitous expression and secretion. However, in this condition, serum levels of mature calcitonin, which is only produced by thyroidal c-cells, remain normal or are only slightly increased.
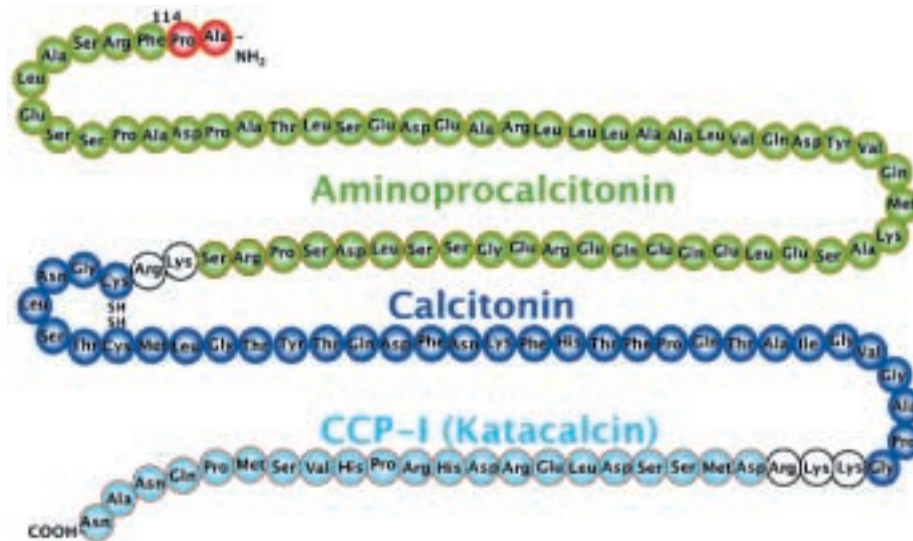


**Figure 2**

Schematic diagram of CALC I expression in adipocytes and thyroidal C cells. In the classical neuroendocrine paradigm, the expression of CT mRNA is restricted to neuroendocrine cells, mainly C cells of the thyroid. Initially, the 116-amino acid pro-hormone ProCT is synthesised and subsequently processed to the considerably smaller mature CT. In sepsis and inflammation, both proinflammatory mediators and bacterial toxins induce CT mRNA, which can be attenuated by interferon γ. In contrast to thyroidal cells, parenchymal cells (eg liver, kidney, adipocytes and muscle) lack secretory granules, and hence, unprocessed ProCT is released in a non-regulated, constitutive manner. Adapted from [13].
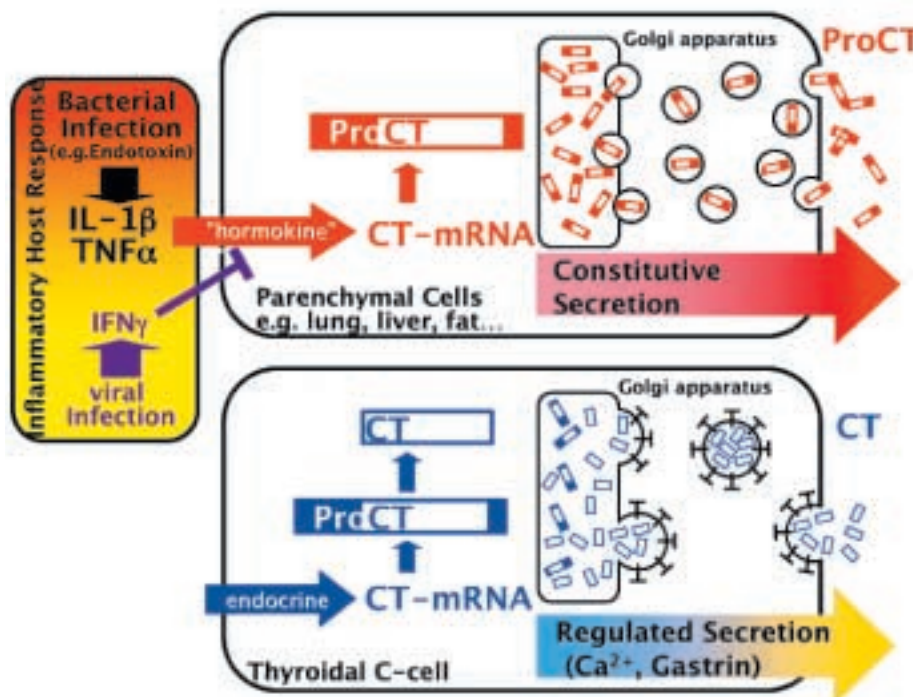
septic circumstances, the entire body could be viewed as being an endocrine gland. Indeed, the transcriptional expression of CT-mRNA is more uniformly up-regulated in sepsis than are the mRNAs of the classical cytokines (eg, tumour necrosis factor (TNF)-α and interleukin (IL)-6). There is a relatively low and only transient expression of ProCT in the white blood cells [14–16]. Importantly, no CT gene expression is found if these cells are harvested from septic patients with markedly elevated serum ProCT levels. In whole blood, LPS-stimulation is unable to induce any detectable ProCT production by leukocytes. Moreover, high serum ProCT levels in septic patients after near-complete eradication of the leukocyte population by chemotherapy suggest that these cells are not a major source of ProCT. Parenchymal cells (including liver, lung, kidney, adipocytes and muscle) provide the largest tissue mass and principal source of circulating ProCT in sepsis [13]. The greater ProCT mRNA induction and

ProCT peptide release from parenchymal cells in comparison to circulating cells, appears to indicate a tissue based, rather than a leukocyte based mechanism of host defense. Thus, CALC-gene products are a prototype of hormokine mediators and can follow either a classical hormonal expression in neuro-endocrine cells or, alternatively, a cytokine-like ubiquitous expression pathway in various cell types [14]. The inflammatory release of hormokines can be induced either directly via microbial toxins (eg, endotoxin) or indirectly via a humoural or cell-mediated host response (eg IL-1β, TNF-α, IL-6). The induction can be attenuated by cytokines also released during a viral infection (eg, interferon-γ). In sepsis, the predominance of ProCT as opposed to mature CT is indicative of a constitutive pathway within cells lacking secretion granules and, hence, a bypassing of much of the enzymatic processing [13]. Consequently, as is the case for most cytokines, there is very little intracellular storage of ProCT in sepsis [14].

## How to measure ProCT levels

For the diagnosis of infections, the diagnostic accuracy of ProCT and its optimum cut-offs are completely dependent on the use of a sensitive assay in a predefined clinical setting (figure 3). Ideally, an ultra-sensitive assay should reliably measure circulating concentrations of ProCT in all healthy individuals. Such assays are currently available for research purposes (PCT sensitive® and N-ProCT^KLB) and should be made widely available for the clinician in the near future. A rapid assay assures that results can be timely incorporated into clinical decision making.

We recently evaluated a newly developed ProCT assay for the guidance of antimicrobial therapy in lower respiratory tract infections [17]. This commercially available assay takes advantage of a time-resolved amplified cryptate emission (TRACE) technology (Kryptor® PCT, Brahms, Hennigsdorf, Germany). It is based on a sheep polyclonal anti-calcitonin antibody and a monoclonal anti-katacalcin antibody, which bind to the calcitonin and katacalcin sequence of calcitonin precursor molecules. The assay has a functional assay sensitivity of 0.06 μg/L, ie 3- to 10-fold above

**Figure 3**

The importance of the procalcitonin (ProCT) assay used. The cut-offs for antibiotic use in respiratory tract infections (RTI) were validated in intervention trials. Importantly, these cut-off ranges are dependent on the clinical context and have to be adapted accordingly (eg lower cut-off ranges with markedly impaired pulmonary reserve, higher cut-off ranges in patients with systemic inflammatory response syndrome on an intensive care unit).
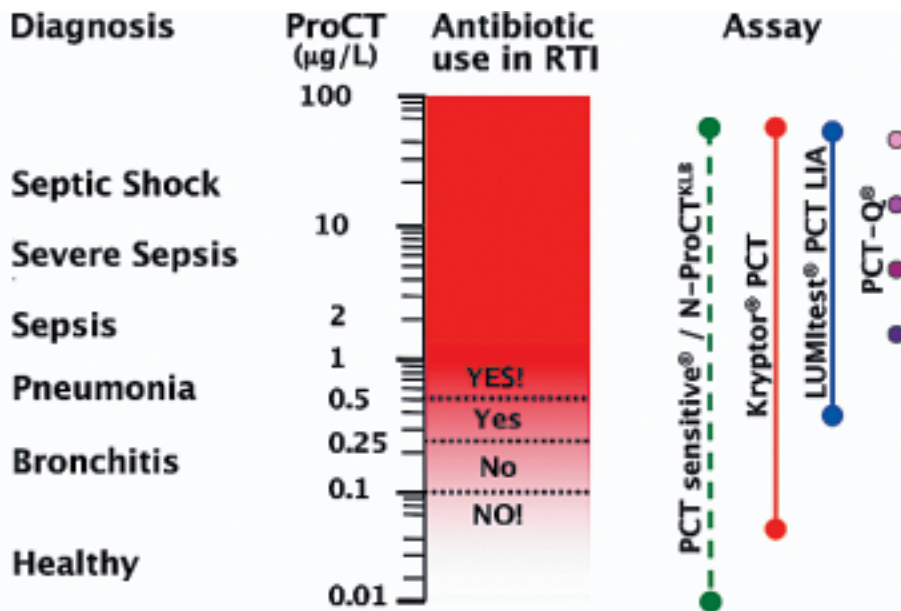
normal mean values [18]. Assay time is 19 minutes and in clinical routine results can be obtained within one hour using 20 to 50 µL of plasma or serum [19]. Another commercially available two-site assay (LUMItest® PCT, Brahms), measures both ProCT and the conjoined CT:CCP I by means of a luminometer. This assay is useful to detect markedly elevated ProCT levels in severe, systemic bacterial infections, ie in sepsis. However, this manual assay has the disadvantage of a relative insensitivity, with an accurate detection limit of ~0.3 to 0.5 µg/L [10,18]. Thus; the LUMItest® assay is not sensitive enough to detect mildly or moderately elevated ProCT levels, which limits the diagnostic use in conditions other than overt sepsis. A colorimetric, "quick" bedside test (PCT®-Q, BRAHMS, Hennigsdorf, Germany) has the advantage of rapid determination of circulating CTpr levels in 30 minutes. Unfortunately, the assay is only semi-quantitative and is not sensitive enough to detect moderately elevated ProCT levels [20].

## ProCT levels in sepsis

Critically ill patients often manifest a systemic inflammatory response syndrome (SIRS). When SIRS is present and infection is proven or suspected, the term sepsis is used. The traditional clinical signs of infection and the routine laboratory tests in sepsis (eg C-reactive protein [CRP] or white blood cell count) lack diagnostic accuracy and are sometimes misleading. In severe infection, most classical pro-inflammatory cytokines (eg TNF-α, IL-1β, or IL-6) are increased only briefly or intermittently, if at all. Mortality in sepsis remains high, often due to delayed diagnosis and treatment. In view of this diagnostic and therapeutic dilemma, a more unequivocal test for the differential diagnosis of infection and sepsis is of paramount importance. Recently, in an attempt to improve current definitions of SIRS and sepsis, it was suggested to include ProCT as additional diagnostic tool to improve and expedite the difficult clinical diagnosis [21]. This was based on evidence from the literature that in sepsis, ProCT levels increase several fold until several thousand-fold and on admission this increase often correlates with the severity of the condition and with subsequent mortality [11, 12]. A variety of studies and reviews have shown the superior diagnostic accuracy of ProCT as compared to other parameters for the diagnosis of sepsis, independent of the origin of infection (References in [12, 22, 23]). Whereas the increase of other inflammatory markers such as CRP is attenuated by immunosuppressive medication (namely steroids), the diagnostic accuracy of ProCT remains unaffected [24]. In addition, ProCT seems to have an advantage over CRP because of its earlier increase upon infection and a better negative predictive value, as for example shown in children with fever of unknown origin [25].

## ProCT as a tool to guide antimicrobial therapy in respiratory tract infections

The most frequent source of systemic infections is the lung [12]. Lower respiratory tract infections (LRTI), ie, acute bronchitis, acute exacerbations of chronic obstructive lung disease (COLD) or asthma, and immunity acquired pneumonia (CAP), account for almost 10% of the worldwide burden of morbidity and mortality [26]. As much as 75% of all antibiotic doses are prescribed for acute RTIs, in spite of their predominantly viral aetiology [26]. This excessive use of antibiotics is the main cause of the spread of antibiotic-resistant bacteria [27, 28]. Thus, decreasing the excess use of antibiotics is essential to combat the increase of antibiotic-resistant microorganisms [29, 30]. A reduction of antibiotic use results in fewer side effects, lower costs, and, in the long-term, leads to decreasing drug resistance [31]. To limit antibiotic use, a rapid and accurate differentiation of clinically relevant bacterial LRTI from other, mostly viral causes is pivotal. After obtaining the medical history, physical examination, laboratory, and chest x-ray, the clinician is often left with diagnostic uncertainty, because signs and symptoms of bacterial and viral infections widely overlap [32, 33]. The lack of specific markers or a gold standard of clinically relevant bacterial infections contributes to the overuse of antibiotics in LRTI, especially in elderly patients with co-morbidities or critically ill patients.

In the "ProResp"-Study we recently assessed the capability of the sensitive ProCT assay (Kryptor® PCT) to identify bacterial LRTIs requiring antimicrobial treatment [17]. In a randomised intervention trial we compared the routine use of antimicrobial therapy versus ProCT-guided antimicrobial treatment for LRTI. In the ProCT group, the physician was advised to follow the antibiotic treatment algorithm based on the ProCT value [12, 34–36]. Thereby, antibiotic treatment was based on serum procalcitonin concentrations as follows (figure 3): strongly discouraged <0.1 µg/L; discouraged <0.25; µg/L; encouraged >0.25 µg/L;

strongly encouraged >0.5 µg/L. Baseline characteristics were similar in the standard group as compared to the ProCT group. The clinical and laboratory outcome after a mean of 13.0 ± 5.4 days was similar in both groups. In the ProCT group the percentage of patients with LRTI, who received antibiotic therapy was reduced by 46.6%, as compared to the standard group (p <0.001). Antibiotic use could be significantly reduced in all diagnostic subgroups, but most striking in acute bronchitis and acute exacerbations of chronic obstructive pulmonary disease.

Pneumonia is defined as inflammation of the pulmonary parenchyma, which is often caused by a bacterial agent and mirrored in markedly elevated ProCT levels [12, 35]. Antimicrobial therapy must be promptly initiated, because a delay of >8 h in treatment is associated with increased mortality [37]. Unfortunately, bacteria are usually identified in less than 50% of cases and a positive viral serology does not rule out complicating bacterial infection. In the clinical context of CAP, the primary value of ProCT is not the reduction of antibiotic prescription, but to facilitate the differential diagnosis of new or progressing infiltrates. Accordingly, ProCT-guidance could markedly lower the number of antibiotic courses in patients with infiltrates on chest x-ray unrelated to pneumonia. Recently, we could show in the "ProCAP"-study that ProCT guidance in the context of CAP allows to significantly reduce the duration of antibiotic treatment from a median of 12 to 5 days [38]. Furthermore, in ventilator-associated pneumonia,

ProCT has emerged as an early prognostic parameter [39].

It is estimated that only 25% of acute exacerbations of COLD patients benefit from the addition of antibiotic therapy [40]. The appearance of new strains and persistence of bacterial infection may contribute to acute exacerbations of COLD and disease progression, respectively [41]. The majority of acute exacerbations of COLD patients have positive sputum culture results. In the ProCT group this rate was similar in patients in whom antibiotics were given or withheld, as was the outcome. This illustrates the limited diagnostic use of sputum cultures in acute exacerbations of COLD. Most of the patients in whom the ProCT-guided treatment algorithm was overruled, were in the acute exacerbations of COLD subgroup. It remains hypothetical whether these patients indeed profited from antibiotic therapy. Nevertheless, since patients with COLD have an impaired pulmonary reserve and the infection might be locally restricted, a ProCT of <0.1 µg/L as cut-off level to withhold antibiotics is advisable in acute exacerbations of COLD patients with severe disease. This cut-off is currently being investigated in the "Pro-COLD"-study including more than 200 patients with acute exacerbations of COLD. Upper respiratory tract infections are commonly seen in general practice and also often unnecessarily treated with antibiotics. Whether ProCT guidance can reduce antibiotic use in upper and lower respiratory tract infections, in general practice, is also currently being investigated ("PARTI"-study).

## ProCT – a marker for other infectious diseases?

The diagnosis of bacterial infections of extrapulmonary sites remains a challenge for clinicians. The general consensus is not to provide antibiotics for every suspected infection because of emerging issues with bacterial resistance. Therefore, a specific marker for bacterial infection would be helpful. Usual markers such as fever, leucocytosis with increased rate of polymorphonuclear cells (or leucopenia), and elevation of CRP, respectively, are sometimes helpful. A positive culture result has a relatively high specificity, but even this is not a gold standard, because it lacks sensitivity and the results are only available after 2 to 3 days. Despite this fact, many researchers use the positive blood culture plus clinical signs of infection as a positive gold standard, and patients without any clinical evidence plus a negative blood culture as the negative gold standard. This forces all patients to be omitted who cannot be classified unambiguously from the analysis [77]. Such an analysis probably circumvents the problem of misclassification bias, at the price of introducing a new bias.

The results of a recent meta-analysis showed that ProCT is a more accurate marker for systemic

bacterial infections independent of the source as compared to CRP levels, both when differentiating bacterial infections from non-infective causes of inflammation and when differentiating bacterial infections from viral infections [42]. Thereby, pooled sensitivity for ProCT was 88% (95%CI 80–93%), compared with 75% (95%CI 62–84%) for CRP levels. Pooled specificity for ProCT was also significantly higher than for CRP (81%, 95%CI 67–90% vs 67% (95%CI 56–77%). ProCT was also significantly better as compared to CRP in differentiating bacterial infections versus viral infections. Pooled sensitivity for ProCT was 92% (95%CI 86–95%) and for CRP 86% (95%CI 65–95%). Pooled specificities were comparable (73%, 95%CI 42–91%) for ProCT and 70%, 95%CI 19–96%, for CRP.

This superior diagnostic performance of ProCT has been shown for a variety of infections [23, 43], eg for meningitis [11, 44], infectious endocarditis [45, 46], pancreatitis [46–49], and others [36].

Serum ProCT is more accurate than the currently available markers for differentiating between viral and bacterial meningitis in both chil-

dren and adults [50, 51]. Conversely, there is a large overlap of usually determined parameters like glucose, proteins and cells of the cerebrospinal fluid and, to a lesser extent, CRP concentrations.

The variability in the clinical presentation of infectious endocarditis makes the diagnosis a clinical challenge. The use of current imaging techniques in the diagnosis of infectious endocarditis is also suboptimal. For example, echocardiography detected infective endocarditis in only 43 of 500 consecutive patients [52]. A simple blood test to predict the presence or absence of infectious endocarditis in suspected cases would be highly desirable. In acute infectious endocarditis, ProCT levels are significantly higher as compared to patients with other final diagnoses [53]. In a recent study, ProCT was the only significant independent predictor of acute infectious endocarditis on admission in a multivariate analysis, in contrast to other parameters like CRP. The diagnostic accuracy was comparable to that of B-type natriuretic peptide for the emergency diagnosis of heart failure [45, 54]. Using a cut-off of 2.3 µg/L, ProCT for the diagnosis of acute infectious endocrditis had a sensitivity of 81%, a specificity of 85%, a positive predictive value of 72% and a negative predictive value of 92%. A word of caution must be added. In some patients, especially with sub-acute endocarditis, ProCT levels may remain very low [55, 56]. Thus, beyond doubt, the diagnosis of infectious endocarditis, as all other infectious diagnoses, will continue to require a critical clinical awareness, careful patient history, dedicated physical examination and blood cultures in all patients. The use of ProCT, albeit not being a perfect marker, might still help to significantly improve the resource utilisation of diagnostic imaging.

Patients with oedematous or toxic pancreatitis have low concentrations of ProCT whereas patients with infectious pancreatitis have very high ProCT concentrations [46]. This is especially useful for the monitoring of these patients in whom secondary infection of the initial pancreatic focus might necessitate surgical intervention. ProCT levels in pancreatitis may reflect the derangement in gut barrier function (rather than the extent of systemic inflammation) and may hence predict those patients in whom the translocation of bacteria and fungi into dead pancreas with consecutive infected necrosis is more likely [48, 57].

Data on the clinical use of ProCT in diverticulitis or other gastro-intestinal infections are lacking.

In patients with localised infections, ProCT is usually lower as compared to patients with generalised infections and positive blood cultures, as expected. In strictly localised infections there is a pronounced increase in ProCT levels only if the infection involves surrounding tissues or becomes systemic. In a closed focus, ProCT concentrations are only moderately high, as in some cases of infectious arthritis in adults [58].

ProCT in urinary tract infections is useful in the absence of well-identified severity markers [59]. In a paediatric study, ProCT unlike TNF, IL-6, IL-8 or CRP was correlated with the severity of renal scars caused by the infection itself, as assessed by scintigraphy [60].

Malaria is the main infectious condition, other than bacterial infections, in which ProCT concentration is high [61]. Even in simple bouts of malaria without neurologic complications, the levels reached are frequently high. The reason for the increased ProCT levels in malaria patients is probably the elevated TNF$\alpha$ level [62]. It is known that large quantities of ProCT are produced after perfusion of TNF$\alpha$ in humans [63].

## ProCT – More than "just" a marker in bacterial infections?

Importantly, ProCT, likely together with other calcitonin precursors, contribute to the *deleterious effects* of systemic infection. The administration of ProCT to septic hamsters with peritonitis doubled their death rate, reaching levels exceeding 90%. Furthermore, treatment with ProCT-reactive antiserum increased the survival of septic hamsters [64–66]. In addition, a one-hour intravenous immunoneutralisation using an antiserum, reacting specifically with porcine ProCT, improved the physiologic and metabolic parameters of septic pigs, and greatly increased their short-term survival (from 0% to 80%) [67]. Furthermore, recent experiments have demonstrated that such immunoneutralisation is effective even when administered after the animals are moribund [68].

Thus, these observations indicate that ProCT is also a potentially harmful mediator involved in the septic response. It was shown, that ProCT acts as a modulator of the inflammatory / immunologic host reaction [69]. Furthermore, ionised hypocalcaemia is more pronounced with increasing severity of infection, and occurs in parallel with the marked increase of ProCT [70]. In contrast, as mentioned above, serum levels of mature CT are normal or only minimally elevated in sepsis [10, 11, 70].

Several characteristics of ProCT favour this hormokine molecule as a therapeutic target in sepsis. In contrast to the transiently increased classical cytokines, for which immunoneutralisation trials in humans have been disappointing, the massive increase of circulating ProCT persists for several days [71]. Furthermore, ProCT is very frequently increased in overt sepsis, its onset is early (within 3 hr), and the diagnostic accuracy of the measurement should greatly improve patient selection for any study of the therapeutic efficacy of ProCT immunoneutralisation and antibiotic therapy in humans.

# ProCT can be a bad marker for infections!

New tests are developed at a fast rate and the technology of existing tests is continuously being improved. For every diagnostic marker, exaggerated and biased results from poorly designed and reported diagnostic studies can trigger their premature dissemination and lead physicians into making incorrect, potentially dangerous treatment decisions [72]. This is also a major risk for a new and promising marker like procalcitonin.

For example, it has been suggested that a ProCT <0.4 µg/L accurately predicts the absence of bacteraemia in adult patients with acute fever, and antibiotic treatment can be safely withheld until additional diagnostic information becomes available [73]. In our opinion, such data have to be interpreted very cautiously and over-enthusiastic conclusions and the resulting hype are potentially dangerous. Clearly, low levels of ProCT <0.4 µg/L can be seen in subacute infectious endocarditis with bacteraemia. Clinically apparent infections are a sequel of complex and variable interactions between host immune response, microbes and their toxins. Obviously, the resulting clinical syndrome is far too complex to be reduced to a single cut-off of any specific surrogate marker.

The likelihood for bacterial infections indeed increases with increasing ProCT levels. We therefore propagated and successfully validated the use of *cut-off ranges* for the diagnosis of bacterial infections and antibiotic stewardship in several intervention trials (ie, ProResp, ProCAP, ProCOLD, PARTI). The innovative rational in these trials was indeed the concept that diagnosis is not the principle outcome measure in the traditional sense of diagnostic test evaluation. This circumvented the problem of the non-existent diagnostic "gold standard" to decide on the presence or absence of a clinically relevant bacterial infection based on traditional criteria (eg, clinical signs, leukocytosis, culture result). Instead, these intervention studies looked directly at patient outcomes, assuming that if the patient recovered without antibiotics then there was no serious bacterial illness.

Thus, it is now evidence-based, by both, meta-analyses of observational studies and intervention studies that as a surrogate marker ProCT provides valuable additional information for the clinical diagnosis bacterial infections. ProCT, thereby, questions the currently used "gold standards", which explains part of the ongoing controversy. How-

**Table 1**

Some potential limitations and weaknesses of ProCT: a research agenda.

| **The optimal cut-off ranges of ProCT are variable and dependent on** |
| --- |
| – the clinical setting (eg primary care, emergency room, intensive care unit, post-operative or trauma patients |
| – the site and extent of the infection (eg RTI, endocarditis, meningitis, others) |
| – co-morbidites (eg impaired pulmonary reserve, immunosuppression) |
| – the clinical implications drawn (eg diagnosis, prognosis, antibiotic stewardship) |
|   For the majority of infections optimal cut-off ranges remain still to be determined in observational studies and validated in intervention studies. |

| **Common causes of false-negative and false-positive results:** |
| --- |
|   **false-positive** (ie, falsely high levels in the absence of a bacterial infection): |
|     newborns (physiologically) during first days of life [78] |
|     acute respiratory distress syndrome [79, 80] |
|     acute attacks of plasmodium falciparum malaria [61] |
|     systemic fungal infections (eg candidiasis, aspergillosis) [81] |
|     severe mechanical trauma [82] |
|     following surgical trauma [83] |
|     administration of monoclonal or polyclonal anti-thymocyte globulin in the treatment of acute rejection after transplantation [84] |
|     chemical pneumonitis [85] |
|     severe burns and heat strokes [86, 87] |
|     patients with medullary thyroid cancer, small cell cancer of the lung, carcinoid, tumours with paraneoplastic hormone production [88] |
|     inflammation associated with "cytokine storms", eg ILβ, in familial Mediterranean fever, therapeutic infusions of TNFα for melanoma [13, 16] |
|   **false-negative** (ie, falsely low levels in the presence of a bacterial infection): |
|     early course of infections [17] |
|     localised infections [58] |
|     subactue endocarditis [55, 56] |

| **ProCT is not a very early marker of infection** |
| --- |
| Follow-up and re-evaluation of ProCT in clinical suspicion of infection is pivotal |

| **A single ProCT value on admission is not a very good prognostic marker** |
| --- |
|   Although higher in patients who survive as compared to non-survivors, ProCT is rather a diagnostic than a prognostic marker. In contrast, the course of ProCT has prognostic implications [39, 89] |

| **Costs** |
| --- |
|   ProCT is more expensive as compared to other biomarkers (eg CRP), for which, however, no intervention studies exist. |

| **Different assays available with very different test performances** |
| --- |
|   The diagnostic accuracy of ProCT is completely dependent on using a sensitive assay in an appropriate, defined clinical setting [34] |
|   Ultra-sensitive assays to determine subtle elevations of ProCT are not yet widely available. |

ever, it cannot be overemphasised that the diagnostic accuracy of ProCT and its optimal cut-offs are completely dependent on using a sensitive assay in an appropriate clinical setting with a pre-test probability for the presence of a specific infection. ProCT is never a substitute for a careful history and physical examination. A clinician should withstand the temptation to rely solely on the result of a laboratory test rather than to interpret a demanding clinical examination.

As is the case for all diagnostic tests, a serum ProCT level must always be evaluated and re-evaluated during follow-up, respectively, with proper regard to the clinical context. The potential limitations and weaknesses of ProCT are summarised in table 1. Importantly, circulating ProCT levels can be increased in non-infectious conditions, and may remain relatively low even in sepsis induced by bacterial infections [34, 36, 74]. In cases of falsely high ProCT levels, in the absence of an infection (typically seen after severe trauma or surgery), ProCT levels are usually moderately elevated between 1 and 10 µg/L, but decline rapidly to values below 1 µg/L within 48 hours. Persistently high ProCT levels in these patients make again the presence of a complicating bacterial infection likely. Conversely, falsely low ProCT levels (typically seen during the early course or localised state of an infection) often show a gradual increase during follow-up measurements after 6 to 24 hours and thereby point to an underlying bacterial disease. This again, stresses the importance of follow-up measurements. Further studies for the comparison of ProCT with other emerging and promising diagnostic markers of bacterial infections (eg soluble triggering receptor expressed on myeloid cells [sTREM]) are strongly encouraged [75]. It is likely that other biomarkers can complement the diagnostic and prognostic power of ProCT.

## Conclusions

An ideal marker for bacterial infections should allow an early diagnosis and should inform about the course and prognosis of the disease. The current *hype* on ProCT has indeed a solid scientific basis, since ProCT covers these features better than many other markers, such as C-reactive protein and proinflammatory cytokines [42]. ProCT has emerged as reliable marker and important mediator of sepsis.

Most sepsis is caused by respiratory tract infections (RTI). A ProCT-based therapeutic strategy can reduce antibiotic usage in RTIs, using a new rapid and sensitive assay. A recent meta-analysis confirmed the higher sensitivity and specificity as compared to CRP both for differentiating bacterial infections from non-infective causes of inflammation and for differentiating bacterial infections from viral infections. Thus ProCT provides *hope*, for an improved diagnostic assessment, antibiotic stewardship and ultimately prognosis of bacterial infections. In addition, being a hormokine mediator, immunoneutralisation of ProCT might open new therapeutic avenues for new treatment options in sepsis.

Beyond any doubt, the diagnosis of infections will continue to require a critical clinical awareness, careful patient history, dedicated physical examination, and appropriate cultures in all patients. However, the interpretation of the clinical response to a bacterial infection lacks standardisation and validation and is, therefore, prone to inter-observer variability [76]. In this context, the measurement of ProCT is considerably *more*, namely, a standardised and evidence-based method for the assessment of patients with suspected bacterial infections. Accordingly, one should question the routine use of "traditional" markers of inflammation (eg white blood cell count, CRP) for which data on diagnostic accuracy are mostly disappointing, if available at all.

Conversely, ProCT is *less* than a perfect marker for bacterial infection and we oppose the uncontrolled use of procalcitonin as a substitute for a careful clinical assessment.

Importantly, any observational study investigating the diagnostic accuracy of a given marker is biased by the choice of the "gold standard". In infections this gold standard does not exist, and thus, all studies are prone to a potential bias. Despite decades of research, this problem has not been solved. Importantly, interventional studies, in which the antimicrobial therapy is guided by the marker and in which the gold standard is the outcome, have the potential to resolve this dilemma. The time has arrived, to conduct more intervention studies for other sites of infection, using more sensitive ProCT assays or other, possibly superior, biomarkers to tackle the vicious cycle of antibiotic overuse and emerging multi-resistance.

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