EXPERT REVIEWS

Procalcitonin for guidance of antibiotic therapy

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Procalcitonin is a surrogate biomarker for estimating the likelihood of a bacterial infection. Procalcitonin-guided initiation and termination of antibiotic therapy is a novel approach utilized to reduce antibiotic overuse. This is essential to decrease the risk of side effects and emerging bacterial multiresistance. Interpretation of procalcitonin levels must always comprise the clinical setting and knowledge about assay characteristics. Only highly sensitive procalcitonin assays should be used in clinical practice and cut-off ranges must be adapted to the disease and setting. Highly sensitive procalcitonin measurements, embedded in diagnosis-specific clinical algorithms, have been shown to markedly reduce the overuse of antibiotic therapy without increasing risk to patients in 11 randomized controlled trials including over 3500 patients from different European countries. In primary care and emergency department patients with mild and mostly viral respiratory infections (acute bronchitis), the initial prescription of antibiotics was reduced by 30–80%. In hospitalized and more severely ill patients with community-acquired pneumonia and sepsis, the main effect was a reduction of the duration of antibiotic courses by 25–65%. This review aims to provide physicians with an overview of the strengths and limitations of procalcitonin guidance for antibiotic therapy when used in different clinical settings and in patients with different underlying infections.

Keywords: antibiotic guidance • pneumonia • procalcitonin • respiratory tract infection • sepsis

The host defense response during systemic infections is characterized by a complex interaction of pro- and anti-inflammatory mediators aimed at combating invading pathogens. Mature forms, precursors and degradation products of these different mediators relocate from the initial site of action into the circulation, where they can be measured. Different mediators display measurable features such as the specific time profile of upregulation upon infection and decrease upon recovery, sensitivity to inflammatory stimuli and specificity for bacterial infection. Based on these characteristics, some markers have more or less potential for clinical applications than others.

There is a large body of evidence that supports the characteristics of procalcitonin (PCT) as a superior marker of severe bacterial infections. The dual function of PCT as a precursor peptide from the hormone calcitonin, and a cytokine mediator, which is elevated upon systemic bacterial infections in line with other cytokines, has led researches to coin the term 'hormokine' mediator [1]. PCT is released ubiquitously in response to microbial toxins and certain bacterial-specific proinflammatory mediators (i.e., IL-1b, TNF-α and IL-6). Thus, a strong correlation between the concentration of PCT and the extent and severity of bacterial infections can be observed [2]. Conversely, PCT levels are attenuated by the cytokines typically released in response to a viral infection (INF-γ). This provides a diagnostic lead to distinguish bacterial infections from viral illnesses [3–5].

As a diagnostic marker, PCT has several advantages over other inflammatory markers. PCT shows a prompt increase upon initial infection within 6–12 h. Conversely, circulating PCT levels halve daily when the infection is controlled by the host immune system and antibiotic therapy. PCT correlates with severity of infection and thus has prognostic implications as well. The course of PCT predicts the risk for mortality in patients with community-acquired pneumonia (CAP) [6], in critically ill patients with sepsis [7] and in patients with ventilator-associated pneumonia (VAP) [3,7–9]. Furthermore, the production of PCT, in contrast to other biomarkers, is not attenuated by non-steroidal and steroidal anti-inflammatory drugs. A study including 102 critically ill patients with systemic infections in a medical intensive care unit (ICU) found significantly lower C-reactive protein (CRP) and IL-6

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levels, but similar PCT levels, in patients treated with systemic corticosteroids compared with untreated patients [8]. These observations were confirmed in healthy male volunteers who received different doses of prednisolone before sepsis was induced with *Escherichia coli* lipopolysaccharide injections. While other biomarkers were significantly inhibited in a dose-dependent manner, levels of PCT showed no inhibition within the study period [10]. These results are of particular importance, for example, in patients treated with systemic corticosteroids for exacerbation of chronic obstructive pulmonary disease (ECOPD) and septic shock. In addition, PCT production does not rely on white blood cells, and in neutropenic patients PCT increases upon bacterial infection [11].

Other surrogate markers have been proposed to diagnose the presence of bacterial infections and guide antibiotic therapy. These include soluble triggering receptor expressed on myeloid cells-1 (s-TREM-1), [12,13] CRP [14] and white blood cell count [15]. However, the usefulness of these markers for guiding antimicrobial therapy in the hospital setting is not supported by controlled intervention trials and has been hampered by low specificity, a delayed response with late peak levels, the need for invasive sampling of bronchoalveolar fluid (s-TREM-1) and their modulation by anti-inflammatory drugs [3,8,16]. These tests therefore have suboptimal practicability and diagnostic accuracy, especially in patients where systemic inflammation is present [13,17–19].

Importantly, unlike other diagnostic biomarkers such as CRP, there is strong evidence from animal studies demonstrating that PCT plays a pathophysiological role in the development of severe sepsis and sepsis-associated mortality. Administration of PCT to septic hamsters with peritonitis doubled their death rate [20]. Conversely, treatment with PCT-reactive antiserum increased survival of septic hamsters and pigs, with mono- and polymicrobial sepsis, respectively [20–23]. A 1 h intravenous immuno-neutralization of porcine PCT improved all vital parameters of septic pigs: it increased short-term survival from 0 to 80% and was effective even when administered after the animals were moribund [21].

Thus, PCT appears to be a preferable marker for diagnosing bacterial infections and an excellent candidate for antibiotic stewardship in patients with systemic infections.

Diagnostic accuracy studies: the challenge of evaluating a diagnostic marker without a gold standard

The first report of increased levels of calcitonin precursor in the setting of an infection was published in 1975 by Canale *et al.* in a case report of superinfected pancreatitis with ensuing hypocalcemia [24]. In 1983, a report by Chesney *et al.* associated elevated levels of calcitonin precursors with pathogenic mechanisms of the hypocalcemia of staphylococcal toxic-shock syndrome [25]. Assicot and colleagues were the first to identify increased PCT concentrations in bacterial infections and meningitis and were the first to observe a rapid decrease upon antibiotic therapy and recovery [26]. Subsequently, researchers from around the world investigated the diagnostic usefulness of PCT for various infections in different clinical settings. Unfortunately, the power of all these observational studies was limited by the heterogeneity of their quality, included patients groups and disease spectrum, and by their use of insensitive PCT assays. *Per definitionem*, observational studies are limited by observer bias, selection bias and issues of sample availability, coinfection, colonization and difficulty of pathogen identification due to time duration, which explains the wide variation of study results.

In conventional diagnostic accuracy studies, the usefulness of a novel test is determined by comparing the results with the definite diagnosis ascertained by the gold standard. The presence of a diagnostic gold standard or reference standard pertains to the best available method for establishing the presence or absence of a disease [27,28]. Observational studies use the ambiguous clinical and microbiological evaluation of the patient as the alleged gold standard to differentiate infected from uninfected patients. Optimally, a morphological verification such as histopathology or growth of typical pathogens in appropriate cultures can be obtained to establish the 'correct' diagnosis. Regrettably, blood cultures as the alleged gold standard in sepsis or respiratory tract infections (RTIs) lack sensitivity and/or specificity and are only available after a time delay. The causative microorganisms cannot be detected in up to 80% of patients with suspected bloodstream infection [29,30]. Of note, in more than 70% of patients with radiologically confirmed CAP the causative microbe is never identified. Conversely, in patients with both stable and acute COPD, typical respiratory bacterial strains are isolated from sputum in up to 50% of patients, which represents colonization in many of these cases.

Sepsis is a clinical syndrome, not a final diagnosis, encompassing highly heterogeneous groups of disorders varying with respect to the site, bacteriology and even presence of infection, where a true gold standard is lacking [31]. In such a circumstance, two fundamentally different concepts are used [28]. One concept tends to ignore potential dilemmas in the accuracy of the alleged gold standard but assumes a well-defined illness, which is represented by the assumption of a diagnostic test or a clinical diagnosis [28]. Many observational studies in different clinical settings using PCT assays have been published investigating the accuracy of PCT for the diagnosis of sepsis (Figure 1). The majority of these studies used the clinical evaluation of the patient and the presence of the 'septic syndrome', that is, two or more systemic inflammatory response syndrome criteria and suspicion of infection, as the gold standard. Accordingly, these observational studies and resulting meta-analyses [18,32–35] reported, in part, conflicting and confusing results since they were biased by the interpretation of the investigator and thus, should be regarded with caution. The other concept discards alleged gold standards and focuses primarily on the outcomes of patients with or without antibiotic therapy. In the case of RTIs and sepsis, the clinical benefit of PCT can be measured by clinical outcomes of randomized intervention studies, assuming that if the patient recovers without antibiotics, there was no relevant bacterial illness. In our opinion, only randomized controlled trials (RCTs), in which antimicrobial therapy is guided by specific cut-off ranges of biomarkers, and in which the primary measure of efficacy is medical outcome, have the potential to evaluate the ultimate clinical usefulness of a diagnostic biomarker.

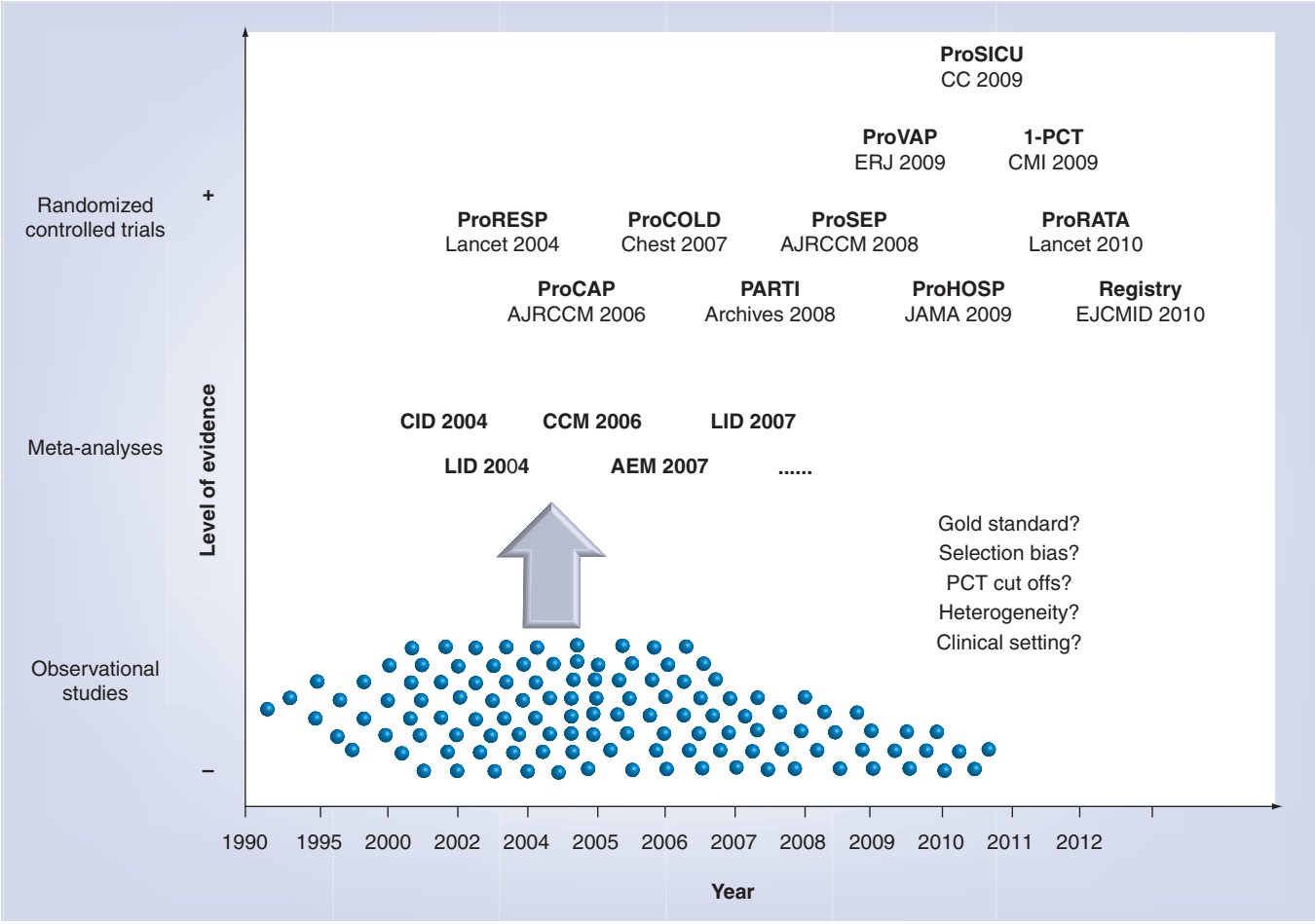
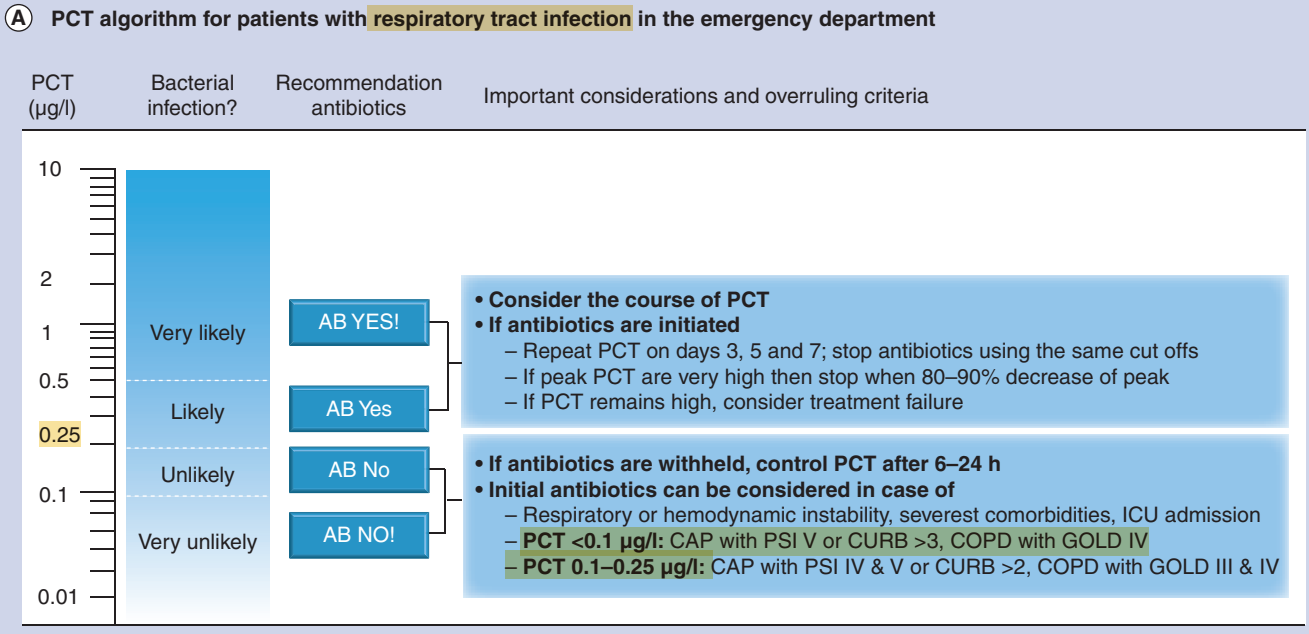


Figure 1. A multiplicity of observational studies has investigated the diagnostic accuracy of procalcitonin in different clinical settings. These studies used mostly the clinical evaluation of the patient as the alleged 'gold standard' to differentiate true bacterial infection from noninfection. Patient selection, differences in clinical setting, differences in underlying diagnoses of patients and in functional sensitivities of PCT assays may lead to the confounding and explain the heterogeneity of study results. Different meta-analyses drew different and even opposite conclusions depending on the inclusion of underlying observational studies. Only RCTs, in which antimicrobial therapy is guided by PCT and in which the primary measure of efficacy is the medical outcome of patients, have the potential to resolve this dilemma and evaluate the clinical usefulness of PCT-guided antibiotic stewardship.
AEM: *American Journal of Emergency Medicine*; AJRCCM: *American Journal of Respiratory and Critical Care Medicine*; Archives: *Archives of Internal Medicine*; CC: *Critical Care*; CCM: *Critical Care Medicine*; CID: *Clinical Infectious Diseases*; CMI: *Clinical Microbiology and Infection*; EJCMID: *European Journal of Clinical Microbiology & Infectious Diseases*; ERJ: *European Respiratory Journal*; JAMA: *Journal of the American Medical Association*; LID: *Lancet Infectious Diseases*; PCT: Procalcitonin; RCT: Randomized controlled trials.

Key points of PCT algorithms for antibiotic stewardship

When PCT is used to guide diagnostic and therapeutic decisions in patients with infections in medical practice, two important issues need to be considered in order to optimize diagnostic accuracy and the safety of patients: the functional assay sensitivity and the cut-off ranges.

Older diagnostic studies used the BRAHMS LUMI test (BRAHMS Aktiengesellschaft, Hennigsdorf, Germany) to measure PCT levels, which detects only markedly elevated PCT levels with a luminometer (functional assay sensitivity: 0.3–0.5 µg/l). This assay with a limited sensitivity in the low range should not be used in clinical practice, for example, in patients with RTI or early and mild infections at other sites [36]. All studies using these insensitive assays must be interpreted prudently as reported PCT levels less than 0.5 µg/l are not accurate. A more sensitive PCT assay with a lower detection limit of 0.06 µg/l is the BRAHMS Kryptor assay (BRAHMS Aktiengesellschaft), which is based on a sheep polyclonal anti-calcitonin antibody [37]. Results can be obtained within 1 h and approximately 20–50 µl of plasma is needed for one measurement. This highly sensitive assay was used in most intervention studies of lower RTI (LRTI) and sepsis to aid in antibiotic stewardship. Recently, other quantitative automated options for PCT testing have become available, including the VIDAS system (bioMérieux, France) [38], the Liaison BRAHMS PCT (DiaSorin, Italy) [39] and the Elecsys BRAHMS PCT (Roche Diagnostics, Basel, Switzerland) [40]. A comparison study using samples from two previous intervention studies [41,42] conducted



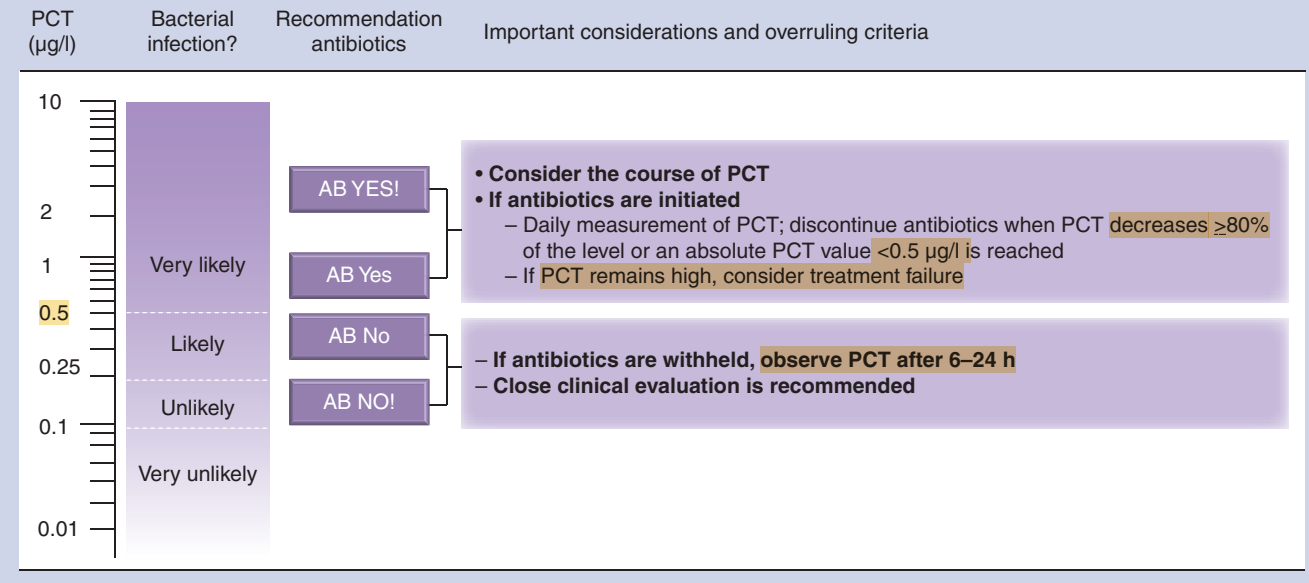


Figure 2. Procalcitonin algorithm in patients with (A) respiratory tract infections in the emergency department and (B) sepsis in the intensive care unit. The clinical algorithm for antibiotic stewardship in patients with respiratory tract infections in the emergency department encourages (>0.5 or >0.25 µg/l) or discourages (<0.1 or <0.25 µg/l) initiation or continuation of antibiotic therapy more or less based on PCT-specific cut-off ranges. In critically ill patients in the intensive care unit, cut offs need to be adapted and antibiotic therapy should be encouraged in patients with levels ≥0.5 or ≥1.0 µg/l, and discouraged in patients with levels <0.5 or <0.25 µg/l, respectively. AB: Antibiotic; CAP: Community-acquired pneumonia; LRTI: Lower respiratory tract infection; PCT: Procalcitonin; PSI: Pneumonia Severity Score.

on the VIDAS system showed a high correlation and concordance with the established BRAHMS Kryptor method, which supports the use of the same nominal PCT cut-off ranges previously established with the BRAHMS Kryptor [38].

All published studies on antibiotic stewardship used similar clinical algorithms with recommendations for and against antibiotic treatment based on PCT cut-off ranges. The algorithms specified one of four antibiotic recommendations, ranging from 'strongly

Table 1. Overview of intervention studies using procalcitonin for guiding antibiotic therapy.

Authors	Study name	Research question	Setting	n	Mortality (n; control versus PCT group)	Overall AB exposure (control versus PCT group)	Relative antibiotic reduction (%)	Ref.
Christ-Crain *et al.*	ProRESP	Reduction of antibiotic prescription for LRTI in the ED?	ED, single center	243	4 vs 4	10.7 vs 4.8†	55.1	[41]
Christ-Crain *et al.*	ProCAP	Reduction of antibiotic exposure in CAP in ED and hospital?	ED and hospital, single center	302	20 vs 18	12.9 vs 5.7†	55.8	[42]
Stolz *et al.*	ProCOLD	Reduction of antibiotic exposure in COPD exacerbation over 6 months?	ED, single center	208	9 vs 5	7.0 vs 3.7†	47.1	[48]
Briel *et al.*	PARTI	Safety and reduction of antibiotic exposure in upper and lower RTI?	Primary care, multicenter	458	1 vs 0	6.8 vs 1.5†	77.9	[59]
Nobre *et al.*	ProSEP	Reduction of antibiotic exposure in sepsis in the ICU?	ICU, single center	79	8 vs 8	9.5 vs 6‡	36.8	[44]
Schuetz *et al.*	ProHOSP	Safety and feasibility in LRTI in a multicenter setting?	ED and hospital, multicenter	1359	33 vs 34	8.7 vs 5.7†	34.5	[49]
Stolz *et al.*	ProVAP	Reduction of antibiotic exposure in VAP in different ICUs ?	ICU, multicenter	101	12 vs 8	9.5 vs 13§	27	[62]
Kristoffersen *et al.*	1-PCT	Reduction of antibiotic exposure for LRTI in Denmark?	ED and hospital, single center	210	1 vs 2	6.8 vs 5.1†	25.0	[52]
Hochreiter *et al.*	ProSICU	Guiding antibiotic therapy with PCT in a surgical ICU?	Surgical ICU, single center	110	14 vs 15	7.9 vs 5.9†	25.3	[46]
Bouadma *et al.*	ProRATA	Reduction of antibiotic exposure for sepsis in different French ICUs?	ICU, multicenter	621	64 vs 65¶	11.6 vs 14.3§	23	[45]
Total				**3691**	**166 vs 159**			

†Mean.
‡Median.
§Antibiotic-free days.
¶30 days mortality rate.
AB: Antibiotic; ED: Emergency department; ICU: Intensive care unit; CAP: Community-acquired pneumonia; COPD: Chronic obstructive pulmonary disease; LRTI: Lower respiratory tract infection; PCT: Procalcitonin; RTI: Respiratory tract infection; VAP: Ventilator associated pneumonia.

discourage' and 'discourage' to 'recommended' and 'strongly recommend', respectively. The PCT cut-off ranges were derived from multilevel-likelihood ratio calculations obtained in observational studies and reflect the likelihood of a bacterial infection [30]. The feasibility and safety of these algorithms was prospectively investigated and repetitively validated in multiple RCTs by independent groups. Namely, in LRTI, initiation or continuation of antibiotics was more or less discouraged (<0.1 or <0.25 µg/l) or encouraged (>0.5 or >0.25 µg/l), respectively (Figure 2) [43]. In case antibiotics were withheld, clinical re-evaluation and a repeated measurement of PCT were recommended after 6–24 h if the clinical condition did not improve spontaneously. If PCT values were increased and antibiotic therapy was initiated, repeated PCT measurements after 2–3 days were recommended and antibiotics were discontinued using the same cut-off ranges. In patients with very high PCT values on admission (e.g., >10 µg/l), discontinuation of antibiotic therapy was encouraged if levels decreased by 80–90% of the initial value. To assure safety, specific 'overruling' criteria were predefined, where this algorithm could be bypassed (most importantly life-threatening disease or immediate need for ICU admission). Physicians were advised that persistently elevated PCT levels may indicate a complicated course, while PCT levels may remain relatively low in localized infections (e.g., empyema or abscess).

For sepsis in the ICU setting, the algorithm used was similar to guide the duration of antibiotic course upon clinical stabilization of the patient. The cut-off ranges were adapted to the higher

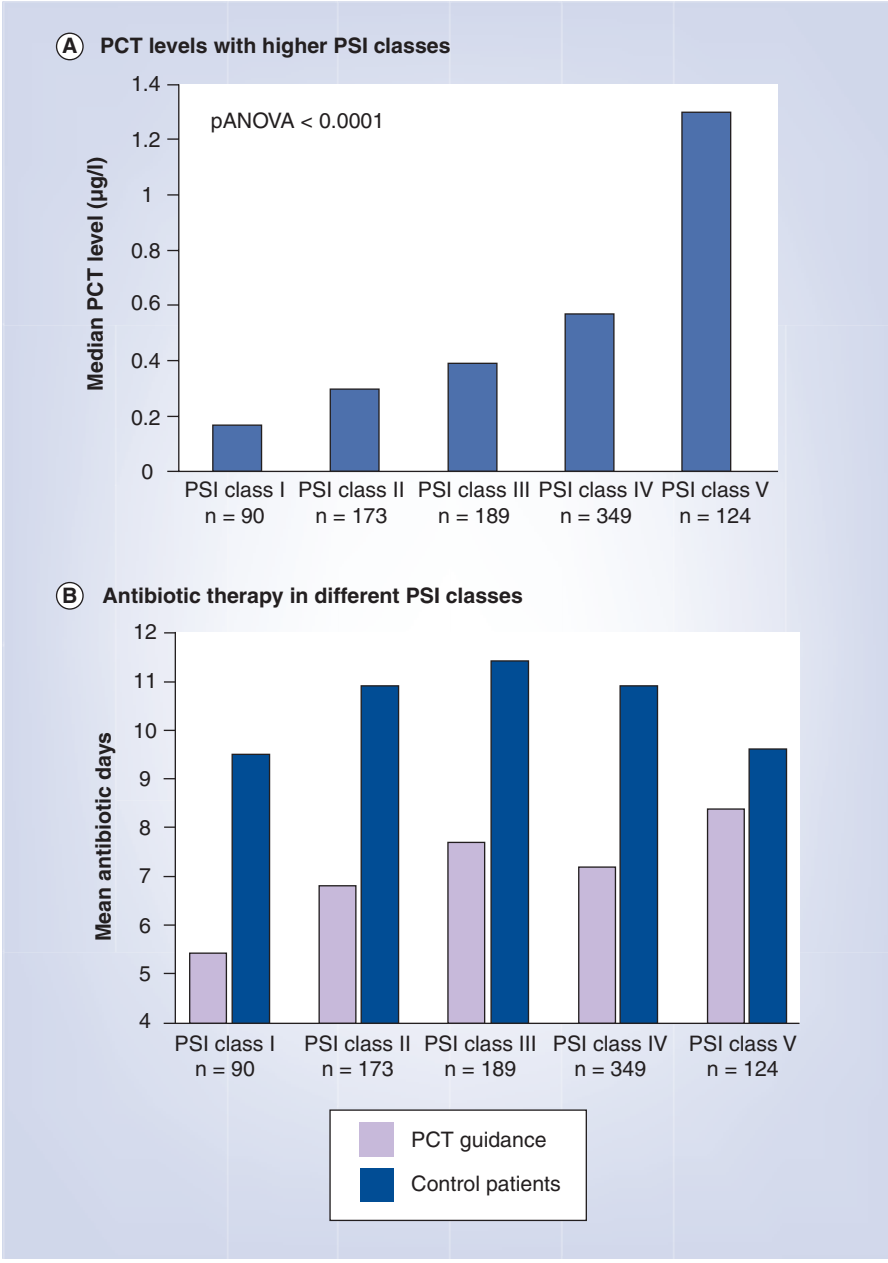


Figure 3. Procalcitonin concentrations displayed approximately an eightfold increase with increasing severity of community-acquired pneumonia based on Pneumonia Severity Index score in the ProHOSP study. Consequently, duration of antibiotic therapy was different in different severities of community-acquired pneumonia in the PCT group, while in the control group antibiotic courses were similar. pANOVA: p-value from analysis of variance; PCT: Procalcitonin; PSI: Pneumonia Severity Score.

PCT levels of patients with severe sepsis, while early and empirical initiation of antibiotics and other supportive therapies are of paramount importance in a critically ill patient on admission and are not questioned by this algorithm. Nobre and colleagues treated all patients with sepsis on admission to the ICU, but used PCT cut offs for early discontinuation of therapy [44]. Patients with a baseline PCT level of 1 µg/l or more were re-evaluated at day 5 and antibiotics were stopped when PCT dropped by more than 90% from the baseline peak level, or an absolute value below 0.25 µg/l was reached. Patients with a PCT level below 1 µg/l at baseline were re-evaluated at day 3, and treating physicians were encouraged to discontinue antibiotics when the PCT level was below 0.1 µg/l and careful clinical evaluation ruled out severe infection. Similarly, the Procalcitonin Reduce Antibiotic Treatments in Acute-Ill Patients (PRORATA) study algorithm specified that when baseline PCT was less than 0.25 µg/l or 0. 25 µg/l or more, but less than 0.5 µg/l, antibiotics were 'strongly discouraged' or 'discouraged', respectively [45]. When baseline PCT was 0.5 µg/l or more but less than 1 µg/l or 1 µg/l or more, starting antibiotics were 'encouraged' or 'strongly encouraged', respectively (Figure 2). When antimicrobials were withheld, clinical re-evaluation and repeated PCT measurements were recommended to detect a late PCT level peak, which thus avoided withholding antibiotics from patients with true bacterial infections. In a trial including septic patients from a surgical ICU, PCT cut offs were further adapted and antibiotic therapy in the PCT-guided group was discontinued if clinical signs and symptoms of infection improved and PCT decreased to less than 1 µg/l, or if the PCT value was more than 1 µg/l, but had dropped to 25–35% of the initial value over 3 days [46].

PCT-guided antibiotic therapy in RTIs

Some physicians use clinical signs such as defervescence, decreased sputum production and coughing, or improvement of general condition to guide duration of antibiotic therapy in LRTI. However, the interpretation of the clinical response lacks standardization and validation and is prone to interobserver variability [47]. In this context, most experts agree that an accurate and readily measurable biomarker like PCT, which predicts the severity and extent of a bacterial infection, would be helpful. The first intervention study testing the hypothesis that PCT can be used to guide antibiotic therapy in individual patients with LRTI as a surrogate biomarker in the emergency department was the ProRESP trial [41]. In this study, 243 patients with different LRTIs were included (CAP = 87, ECOPD = 69, acute bronchitis = 59, asthma = 13 and other LRTI = 24). Clinical outcomes for both groups were similar, but the PCT-guided group had markedly lower rates of antibiotic prescriptions (44 vs 83%), particularly in patients with ECOPD

and acute bronchitis (Table 1). In patients with radiological evidence of CAP, 90% of patients in the PCT group received antibiotics primarily due to increased PCT levels in the majority of these patients. On the basis of these findings, two subsequent prospective RCTs were initiated to evaluate the effect of PCT guidance for antibiotic discontinuation in CAP ('ProCAP') and to assess safety over a 6 month follow-up in ECOPD patients ('ProCOLD'), respectively. The ProCAP study included 302 patients with radiologically confirmed, mostly severe CAP with more than 60% of patients in Pneumonia Severity Index (PSI) classes IV and V [42]. PCT guidance only reduced the initial prescription rate by about 10%, but shortened the duration of antibiotic therapy by 65% with a similar outcome in patients with all severities of CAP. An important finding of the study was that only in the PCT group, and not in the control group, was the duration of antibiotic course adequately tailored to the severity of the disease, being longer in patients with higher PSI scores and in patients with positive blood cultures.

The ProCOLD study included 208 patients with ECOPD [48]. Patients were followed up during hospitalization, at a short-term visit, and throughout the following 6 months. PCT guidance reduced antibiotic prescription from 72 to 40% at the initial exacerbation and the effect was sustained over the 6 month follow-up period (RR: 0.76; 95% CI: 0.64–0.92). Importantly, clinical outcomes, improvement in forced expiratory volume in 1 s (FEV_1) and exacerbation rates over 6 months were similar in both groups, which suggested the safety of a PCT-guided antibiotic algorithm in ECOPD patients. The aforementioned trials showed promising results for the concept of PCT guidance in LRTI. However, remaining limitations needed to be addressed, including external validity in a multicenter setting, enforced implementation of guidelines in the control group and the ultimate proof of safety in terms of adverse outcomes in a large and adequately powered sample of patients. For this reason, the multicenter ProHOSP trial was initiated. A total of 1381 patients in six Swiss hospitals were included and the study was powered for noninferiority of serious adverse outcomes of patients [43,49]. To optimize adherence to guidelines in the control group, treating physicians were required to follow web-based guidelines for every patient included [43]. The results of ProHOSP confirmed earlier PCT study results: antibiotic exposure was reduced by 32.4% in CAP, by 50.4% in ECOPD and by 65% in acute bronchitis. The paths to reducing antibiotic exposure differed in a predictable fashion: for ECOPD and acute bronchitis, decreased antibiotic exposure was principally from nontreatment, whereas for CAP it was principally from reduction in duration of therapy. Additionally, the reduction of antibiotic exposure translated into a reduction of antibiotic-associated side effects of approximately 30% in PCT-guided patients. The enforcement of guidelines also showed a moderate effect and a reduced duration of antibiotics from 12 to 10 days in CAP control patients when compared with a previous study with less stringent enforcement [42]. Importantly, the overall rate of adverse events was similar in both ProHOSP study arms and excluded a risk of more than 0.4% for PCT-guided patients (confidence interval [CI] for the difference in adverse outcomes: -7.6–0.4). In terms of mortality, the risk was similar in both arms and excluded a risk of more than 2.5% (CI for the difference in mortality: -2.1–2.5). PCT concentrations showed a step-wise increase with increasing severity of CAP as assessed with the PSI score [50] (Figure 3A). This resulted in a longer duration of antibiotic therapy in higher risk patients with higher PSI classes in the PCT group, while in the control group antibiotic courses were similar (Figure 3B). As demonstrated in two previous smaller studies [42,44] and in the ProHOSP study, patients with bacteremic CAP had markedly increased PCT concentrations resulting in longer treatment duration as compared with culture-negative CAP patients with a lower infection-related risk. The time to first antibiotic dose has recently received significant attention from a quality-of-care perspective based on two retrospective studies reporting a reduced mortality in CAP patients who received antibiotic treatment within 4–8 h [51]. Within aforementioned intervention trials, PCT was measured using a rapid sensitive assay and an assay time of approximately 20 min [49]. The results were routinely available around the clock within 1 h and by the time results from routine chemistry were available. Thus, if PCT is measured on admission in patients with suspicion of LRTI, PCT can be used for the evaluation of the patients without putting them at risk because of time delays before initiation of therapy.

The concept of using PCT for guidance of antibiotic therapy in LRTI has now been adapted by clinicians and researchers in other countries. A recent study from Denmark included 223 LRTI patients and reported a reduction of antibiotic therapy of 25% despite the fact that in 41% of cases physicians disregarded the PCT algorithm and continued antibiotic treatment in patients with low PCT levels [52]. Obviously, a high adherence rate to the PCT algorithm is key to having the same effect of PCT guidance in clinical practice as found in controlled studies where adherence is being monitored. It is well known that results obtained in RCTs are frequently inadequately implemented in daily practice. For instance, patients with CAP are often admitted to in-hospital care despite a low risk for mortality as assessed with the PSI and guideline recommendations to treat as outpatients [50,53]. For this reason, an observational quality control survey (PCT Registry) recently investigated the effectiveness of PCT-guided antibiotic stewardship in a 'real life'-setting of a 600-bed hospital outside of study conditions [54]. Of note, the local Institutional Review Board classified this study as essential quality surveillance and waived the need for patient informed consent, which assured a true consecutive enrollment of patients and minimized study-bias by the Hawthorne effect. The survey included 302 consecutive LRTI patients including those with the severest comorbidities: 28% of patients had neoplastic disease and 6% of patients were immunosuppressed. The results of the survey showed that in 73% of patients, antibiotics were administered according to the prespecified PCT algorithm. Antibiotic therapy was significantly reduced in these patients as compared with patients in the same institution who represented the control group receiving antibiotic therapy without PCT guidance in a previous trial (ProHOSP) [49]. The most important overruling reasons were severe immunosuppression (6%), other infections in need of antibiotic treatment (5%) and anticipated complications (3%). In 10% of enrolled patients, the PCT algorithm was not followed without any

pre-specified overruling criteria and because of the clinical judgment of the treating physician. Over time, a decreasing rate of noncompliance with the PCT algorithm was observed. Thus, the survey showed that utilization of the PCT algorithm was feasible and effective in clinical practice, but that the implementation of this algorithm requires time and should be understood as a learning process, where physicians need to become more familiar with the PCT algorithm step by step. Given the critical association between adherence and effectiveness, ongoing reinforcement is required to guarantee the success of intervention and thus ensure patient safety and the rational use of antibiotics.

Currently, a multinational observational quality surveillance study is ongoing in Switzerland, France and the USA (ProREAL, ISRCTN40854211 [101]). All consecutive adults with LRTI who are seen in hospital emergency departments or general practitioner's offices and are being treated in either an ambulatory or hospital setting are registered and monitored for 30 days after diagnosis. The primary aim is to assess the efficacy of PCT-guided antibiotic therapy for patients with LRTI outside of study conditions; secondary goals include assessment of adherence to the PCT algorithm and its safety in a real-life setting.

PCT-guided antibiotic therapy in primary care

Arguably, the most important (over-) use of antibiotics for upper and lower RTI occurs in primary care. As much as 75% of patients with RTI receive antibiotics, despite the mostly viral origin of the condition [55]. The two main reasons for this overuse are that clinical signs and symptoms for bacterial origin of infection, including fever, dyspnea, purulent sputum and white blood cell count, are all nonspecific and not reliable, and that time pressures, which are particularly short in this setting, restrict the application of more complicated decision systems. Thus, differentiation between viral and bacterial RTIs remains difficult. Other major reasons for antibiotic prescription in primary care are nonmedical and related to the physician–patient relationship and patients' expectations and beliefs about the alleged benefit of antibiotics. Different clinical trials have shown the difficulties of changing antibiotic prescription patterns in primary care. Optimizing physician education and practice guidelines disseminated for pharyngitis management showed no effect [56], and nor did a communication intervention in another trial [57].

A biomarker strategy for guiding antibiotic therapy could thus have two different effects: improving the diagnostic ability of the primary care physician and reassuring patients that antibiotics are not necessary. For these reasons, a multicenter primary care trial was initiated in Switzerland to study the safety and feasibility of the PCT-guided algorithm in 450 patients with acute upper and lower RTI who were in need of antibiotics as judged by their primary care physician (PARTI) [58,59]. The primary aim of this study was to demonstrate noninferiority regarding the duration of time in which activities were restricted. Patients whose PCT levels were measured were prescribed antibiotics far less often than those without PCT measurement (25 vs 97%) without differences in the number of days with restricted activities caused by infection, or the risk of ongoing or relapsing infection at 28 days (95% CI: -0.53–0.81 days, which met the noninferiority criterion of an increase in days in which activities were restricted by no more than 1 day). Adverse effects attributable to antibiotics – particularly diarrhea – were more common among patients in the control group. In this study, PCT levels were measured in a central laboratory. A more rapid, office-based version of the PCT assay with acceptable accuracy and at a reasonable cost would certainly facilitate a more broad-scale use of PCT in primary care. Prior to the publication of this review, a study from the German CAPNETZ was published, which found a 42% reduction of antibiotic use in 550 primary care patients and no differences in health impairment when using a similar PCT algorithm, but limited to an initial PCT measurement only [60].

A similar RCT was recently conducted in primary care in The Netherlands with a treatment algorithm based on either CRP levels and/or communication training and was compared with a control group [61]. The authors reported a 42% relative reduction in antibiotic use with CRP guidance, which was similar to the effect of communication training in this setting. However, the usefulness of CRP for antibiotic guidance outside the primary care setting is not supported by controlled intervention trials.

PCT for antibiotic guidance in the ICU

Despite a large body of literature in favor of PCT in the ICU, there has been much debate about the clinical usefulness of PCT measurement in the critical care setting due to the absence of outcome studies. The first small proof-of-concept study in critically ill ICU patients with sepsis that used a similar PCT algorithm to the one used to guide duration of antibiotic therapy in CAP was conducted by ICU physicians in Geneva (ProSEP) [44]. They observed a significant 4-day reduction in the duration of antibiotic therapy in patients with severe sepsis and septic shock in whom a decision could be made based on an algorithm of serial PCT measurements (per-protocol analysis). In the overall population including patients in whom the PCT algorithm was not followed, a trend towards lower antibiotic therapy was found (from 9.5 to 6 days), without reaching statistical significance ($p = 0.15$), however. Interestingly, the researchers found a 2-day shorter ICU stay in patients assigned to the PCT-guided group. Although there was no explicit explanation for this finding, the authors speculated that caregivers considered it safe to discharge their patients from the ICU (and subsequently from the hospital), because no adverse event was observed after earlier than anticipated antibiotic discontinuation.

The concept and safety of PCT guidance in severely ill medical ICU patients was subsequently validated in a large multicenter trial in France in which more than 600 patients were enrolled (ProRATA) [45]. PCT-guided patients had similar 30-day mortality rates (21.2 vs 20.4%; 95% CI of difference: -4.6–6.2), similar rates of relapsing infections (6.5 vs 5.1%; 95% CI of difference: 1.4% [-2.3–5.1]) and similar evolution of the sequential organ failure assessment score, but markedly more antibiotic-free days (14.3 vs 11.6). Duration of antibiotic exposure was significantly reduced in subgroups of patients with CAP (-5.0 days), urinary tract infections (-7.1 days), patients with positive blood cultures (-3.0 days) and in patients with VAP (-2.1 days). As

expected, antibiotic reduction was obtained mainly during the first 10 days by shortening the antibiotic therapy durations, while the diminished antibiotic exposure was only marginal on day 1.

Another multinational ICU study focused on VAP and included 101 patients (ProVAP). PCT determination significantly increased the number of antibiotic free-days within 28 days after VAP onset (13 vs 9.5 days) [62]. This translated into a reduction in the overall duration of antibiotic therapy of 27% without increasing the risk for adverse events.

A German study has recently assessed the effect of PCT guidance in 110 surgical ICU patients with suspected bacterial infections (ProSICU) [46]. PCT guidance resulted in a reduction of antibiotic therapy from 7.9 to 5.9 days and similar medical outcomes. In addition, as observed in the Geneva study, the length of intensive care treatment in the PCT-guided group was significantly shorter than that in the control group (15.5 vs 17.7 days). If this trend towards shorter ICU stays with PCT treatment can be confirmed in larger trials in the near future, we would expect great cost savings.

In terms of cost–effectiveness, more than just the procurement costs of PCT and antibiotic therapy have to be considered. Higher antibiotic use was associated with an increased risk of antibiotic resistance on the population [63], hospital [64] and individual level [65]. In particular, each day of β-lactam use was estimated to result in a 4% increased risk of carrying penicillin-resistant pneumococci in children [66]. By contrast, seasonally decreased antibiotic prescriptions [67] or successful programs to reduce antibiotic use [68] resulted in lower rates of antibiotic resistance to important respiratory tract pathogens. Therefore, it will be interesting to see whether broad-scale application of PCT-guided antibiotic therapy will lead to measurable decreases in antibiotic resistance as predicted. In this case, the value of antibiotics as a nonrenewable natural resource must be taken into account [69]. Future studies should not only address safety and efficacy of PCT for antibiotic stewardship, but should also establish cost–effectiveness by considering country-specific costs of PCT measurement (US$10–30 per sample) and potential savings in consumption of other healthcare resources. For example, in ProHOSP we found initial PCT levels to accurately predict blood culture positivity in CAP patients [70]. Thus, PCT measurement has the potential to reduce the number of blood cultures drawn in the emergency department and to implement a more targeted allocation of limited healthcare resources.

PCT for antibiotic guidance in other infections

Procalcitonin has been put forward as a promising marker to more reliably diagnose true bacterial infections for different types of infections, including neutropenic fever [11], fungal infections [71], post-operative fever [72], arthritis [73], suspected bloodstream infection [74] and many others. Importantly, with the exception of RTIs, meningitis and sepsis within the ICU setting [75], all published studies were observational and it remains uncertain if PCT can safely be used for antibiotic guidance in these different settings. For some infections PCT may not have a sensitivity high enough for use in clinical routine. In patients with sub-acute endocarditis, PCT levels may remain low and do not discriminate infected from noninfected patients [76]. Similarly, in patients with *Mycoplasma* infection, PCT levels may remain low and in the range of viral infections [77], while in other atypical pathogens such as *Legionella pneumophila* PCT showed a prominant increase upon infection [6]. Conversely, in patients with induction of hypothermia after cardiac arrest, high initial values of PCT were found independent of underlying infection [78]. This PCT increase was unspecific and mirrored an inflammatory reaction rather than true infection, limiting the diagnostic potential for early antibiotic stewardship in these high-risk patients.

Escalation of antibiotic therapy based on PCT levels?

The aforementioned ICU studies focused on safely de-escalating antibiotic therapy. Previous studies have shown, however, that mortality rates in ICU patients increase markedly from day-to-day with observed elevation in PCT levels. Thus, PCT measurement can be used to identify patients at risk of complications, treatment failure and associated mortality earlier in the course of the disease [7,9]. The Procalcitonin and Survival Study (PASS study) was initiated to test the hypothesis that daily PCT measurements can precisely monitor the emergence and the course of a serious infection in ICU patients in a timely manner, and via rapid and sufficient changes in the diagnostics and therapeutics can increase the survival rate of patients [79]. The investigators predefined additional diagnostic and therapeutic interventions in cases of high and/or increasing PCT levels. The authors have recently completed the trial and initial results do not seem to support their study hypothesis that escalation of diagnostics and therapeutics can positively influence mortality rates in high-risk patients [80]. Specifically, the authors found that PCT guidance did not improve survival, but the duration of ICU stay and duration of respiratory failure was prolonged. Thus, although elevated or not decreasing PCT levels correctly identify patients at high risk for complications, escalation of antibiotic therapy does not seem to translate into better outcomes for patients.

Prognostic value of PCT

Notwithstanding the potential of PCT as a diagnostic marker, its prognostic impact is debated. Previous studies investigated whether PCT could be helpful for prediction of mortality and other adverse events. While studies in the ICU setting [7,81] and in high-risk *Legionella* CAP patients [6] have demonstrated a high prognostic accuracy of PCT, results from studies in the emergency department with lower severity patients have shown mixed results [6,16,82]. A German study recently found that PCT levels on admission predict severity and outcome of CAP with a similar prognostic accuracy as the CRB-65 score and thereby improve its prognostic ability [82]. A large US-based CAP study found an only moderate additional value of PCT when compared with the PSI and CURB65 scores [83]. PCT did not add prognostic information to the PSI in low-risk PSI classes I–III. However, low PCT levels of less than 0.1 ng/l were associated with significantly lower mortality in high-risk CAP patients as assessed by clinical scores (PSI IV–V and CURB65 3–5). Within ProHOSP, we found a

high prognostic accuracy of PCT for prediction of adverse outcomes and an only moderate accuracy for mortality prediction [Schuetz P, Unpublished Data]. Importantly, repeated measurements of PCT improved the prognostic performance because patients with non-decreasing PCT levels were at higher risk for experiencing adverse outcomes.

Conclusion

Emerging bacterial resistance to multiple antimicrobial agents calls for more effective efforts to reduce the unnecessary and prolonged use of antibiotics in nonbacterial and self-limiting bacterial and resolving diseases [84]. Patients and physicians share the common goal of improving symptoms from infection as fast as possible and often see antibiotics as the most expeditious intervention to achieve it. This one-size fits-all approach for patients with LRTI encompassing self-limiting viral bronchitis and life-threatening CAP fails to consider the basic questions of who benefits from antibiotic therapy, and if treated, what would be the optimal duration. Similarly, sepsis is not a well defined disease but a syndrome, and not all patients who fulfil sepsis criteria are in need of antibiotics urgently or at all. Using PCT, which reflects the likelihood of bacterial infection and the severity of infection, to guide antibiotic therapy is a persuasive new approach to a more rational use of antibiotics.

All observational studies investigating the diagnostic performance of biomarkers in LRTI and in sepsis are hampered by the lack of a true gold standard. Until this is established, only interventional studies, in which antimicrobial therapy is guided by PCT and in which the gold standard is the outcome of patients, have the potential to resolve this dilemma. To date, only PCT has been rigorously assessed in intervention studies for its capability to be used safely for antibiotic stewardship in the hospital setting, providing strong evidence for its diagnostic accuracy. Today, 11 RCTs from different countries enrolling over 3500 patients have demonstrated the feasibility and safety of PCT guidance. In these trials, disease and setting-specific adoption of PCT cut-off ranges are prerequisites for optimal use of PCT in clinical routine. Most intervention studies have been conducted in European countries including Switzerland, Germany, France and Denmark and validation in other countries is therefore warranted. Importantly, PCT levels must always be evaluated in the context of a careful clinical and microbiological assessment. As the kinetics of PCT are of particular diagnostic and prognostic interest, repeated measurements should always be performed, especially in persistently sick patients if antibiotics are withheld. Limitations of every PCT measurement include false-positive and false-negative results [3]. Unspecific elevations of PCT levels in the absence of a bacterial infection can typically be seen in situations of massive stress, for example, after severe trauma or surgery [3,33,72]. In these situations, PCT values are usually only moderately elevated and show a rapid decline in follow-up measurements. Conversely, falsely low PCT levels, typically seen during the early course or localized state of an infection, often show an increase in the follow-up measurements. Therefore, highly sensitive PCT assays are required, as subtle changes of PCT at very low concentrations can be monitored, increasing the sensitivity of the test and thus the safety of patients.

Expert commentary & five-year view

Unnecessary antibiotic usage is a threat to public health owing to increasing bacterial resistance, increased costs and increasing risks for drug-related adverse events. A growing body of literature supports the use of PCT to improve diagnosis of bacterial infections and to guide physicians more effectively to rationally prescribe antibiotic therapy, particularly for RTIs and sepsis. Further intervention studies are needed to define and prospectively validate PCT cut-off ranges for other infectious entities. Knowledge of the strengths and weaknesses of PCT are prerequisites for its rational and safe use in clinical routine. When used within prospectively validated clinical algorithms, PCT is a reliable diagnostic tool for rapid initiation of antibiotic therapy in patients at high risk for severe infections, and for individually stopping therapy earlier depending on the resolution of the infection. To date, the concept of PCT-guided antibiotic therapy has been proven in 11 RCTs including over 3500 patients. This has been recognized by the infectious disease community and the routine measurement of PCT in sepsis has recently been recommended by the German sepsis guidelines. Measurement of PCT should never replace but add to a careful clinical assessment. It does, however, hold great promise for more tailored management of patients with systemic infections, while promoting antibiotic stewardship for the entire population.

Key issues

- The use of procalcitonin (PCT) as a surrogate biomarker is a novel approach to more tailored management of systemic infections and guidance of antibiotic therapy.
- PCT can be used to guide, tailor and thereby reduce antibiotic duration in different settings and infections with similar medical outcomes for patients; to date, its use has been best documented in respiratory tract infections (RTIs) and sepsis.
- PCT guidance has a differential effect on initial prescription and/or duration of antibiotic therapy depending on the severity of infection and the clinical setting.
- Shortening antibiotic exposure has been shown to significantly reduce the risk of antibiotic-related side effects in individual patients and reduce the emergence of multidrug resistance on a population level.
- Based on outcome data of 11 randomized controlled intervention studies enrolling more than 3500 patients, PCT-guided antibiotic therapy is proven to be safe in RTIs and sepsis.
- Further analysis is necessary to evaluate cost–effectiveness of current PCT algorithms in different settings and healthcare systems while considering antibiotics as a natural resource.
- Future intervention trials are needed to broaden the knowledge of PCT guidance in non-European countries, and to expand application in disease states other than RTIs and sepsis. This includes settings where nonbacterial infections such as malaria, which is known to cause high PCT levels, might be considered in the differential diagnosis.

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REVIEW Open Access

Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future

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Abstract

There are a number of limitations to using conventional diagnostic markers for patients with clinical suspicion of infection. As a consequence, unnecessary and prolonged exposure to antimicrobial agents adversely affect patient outcomes, while inappropriate antibiotic therapy increases antibiotic resistance. A growing body of evidence supports the use of procalcitonin (PCT) to improve diagnosis of bacterial infections and to guide antibiotic therapy. For patients with upper and lower respiratory tract infection, post-operative infections and for severe sepsis patients in the intensive care unit, randomized-controlled trials have shown a benefit of using PCT algorithms to guide decisions about initiation and/or discontinuation of antibiotic therapy. For some other types of infections, observational studies have shown promising first results, but further intervention studies are needed before use of PCT in clinical routine can be recommended. The aim of this review is to summarize the current evidence for PCT in different infections and clinical settings, and discuss the reliability of this marker when used with validated diagnostic algorithms.

Background

Emerging bacterial resistance to antimicrobial therapeutics calls for more stringent efforts to reduce antibiotic overuse [1]. Towards this aim, there has been considerable interest in antibiotic stewardship programs aimed at reducing antibiotic overuse by tailoring antibiotic therapy to individual needs of patients [2,3]. Despite the successful implementation of diagnostic biomarkers in different fields of medicine (for example, D-dimers in pulmonary embolism, natriuretic peptides in acute heart failure, troponin in myocardial infarction), accurate and timely diagnosis of bacterial infections remains a challenge [4,5]. Reliable clinical and/or microbiological parameters from easy to obtain specimens that may be used to diagnose bacterial infections and rule out other infections not in need of antibiotic therapy have been largely lacking. The main disadvantages of many current microbiological methods are diagnostic delays (for example, culture methods), suboptimal sensitivity (for example, blood cultures) and low specificity due to contamination (for example, sputum cultures), whereas others are not amenable to routine diagnostics due to their invasive nature (for example, lung biopsy). Inflammatory markers, such as C-reactive protein (CRP) or white blood cells (WBC), lack specificity for bacterial infections [6]. This is partly explained by the heterogeneity of different infections and the complex interaction of different pro- and anti-inflammatory mediators of the host response aimed at combating invading pathogens during systemic infections, which depend on timing, type, extent and site of the underlying infection.

In this diagnostic dilemma, procalcitonin (PCT) has stimulated great interest as a potentially more specific marker for bacterial infection. PCT is produced ubiquitously in response to endotoxin or mediators released in response to bacterial infections (that is, interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6) and strongly correlates with extent and severity of bacterial infections [7]. Because up-regulation of PCT is attenuated by interferon (INF)-γ, a cytokine released in response to viral infections, PCT is more specific for bacterial infections and may help to distinguish bacterial infections from viral illnesses [8-11]. PCT shows a favorable kinetic profile for use as a clinical marker: it promptly increases within 6 to 12 hours upon stimulation and circulating PCT levels halve daily when the infection is controlled by the host immune system or antibiotic therapy [12]. PCT correlates with bacterial load [13-15] and severity of infection [6,16-18]. PCT thus has prognostic implications and the course of PCT

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predicts fatal outcome in patients with community-acquired pneumonia (CAP) [18-21] and critically ill patients with sepsis [22].

Based on this evidence, PCT has been put forward as a promising candidate marker for diagnosis and for antibiotic stewardship in patients with systemic infections [23]. Importantly, as with any diagnostic tool, PCT should be used embedded in clinical algorithms adapted to the type of infection and the clinical context and setting. While for some types of infections and clinical settings optimal PCT cut-offs have been established and their safety and efficacy shown in randomized-controlled intervention trials, for other types of infection only observational studies are available today (Figure 1), and thus the clinical benefit and safety of using PCT remains undefined.

The aim of this review is to summarize the current evidence for PCT in different infections and clinical settings, and discuss the strengths and limitations of PCT, and the reliability of this marker when used with validated diagnostic algorithms.

Procalcitonin as a diagnostic marker: results from observational studies

A plethora of observational studies have investigated the diagnostic potential of PCT in different clinical situations and different types and sites of infections. Table 1 summarizes study designs, proposed PCT cut-offs and main conclusions of selected relevant studies investigating different types of infections. This selection focuses on more recent research and on studies using highly sensitive PCT assays (that is, with a functional assay sensitivity around 0.06 μg/L) [24,25].

For the diagnosis of blood stream infections and bacteremia, studies found a high diagnostic performance of PCT [13-15]. To distinguish blood contamination from true blood stream infection in patients with growth of coagulase-negative staphylococci in their blood cultures,

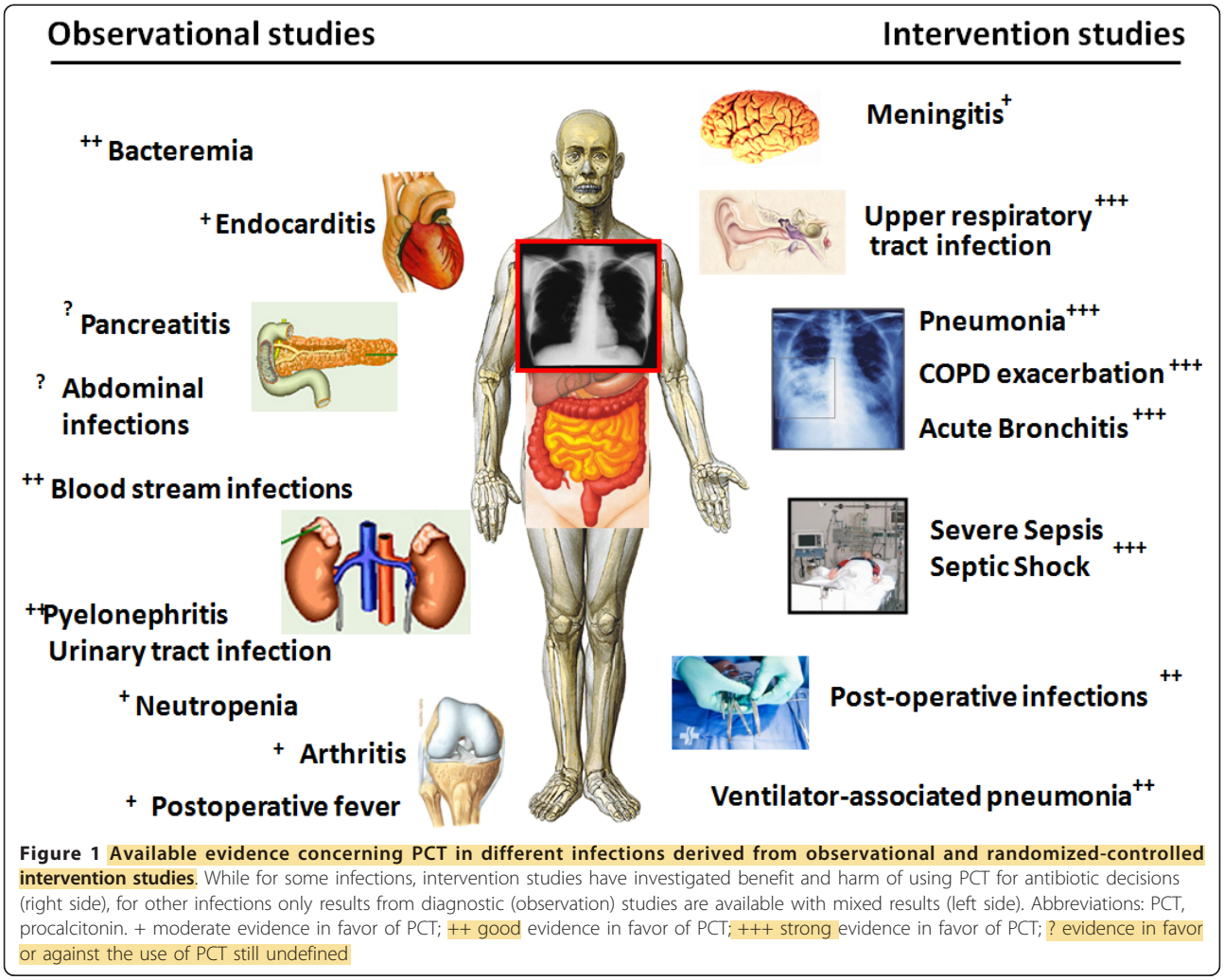

Figure 1 Available evidence concerning PCT in different infections derived from observational and randomized-controlled intervention studies. While for some infections, intervention studies have investigated benefit and harm of using PCT for antibiotic decisions (right side), for other infections only results from diagnostic (observation) studies are available with mixed results (left side). Abbreviations: PCT, procalcitonin. + moderate evidence in favor of PCT; ++ good evidence in favor of PCT; +++ strong evidence in favor of PCT; ? evidence in favor or against the use of PCT still undefined

Table 1 Overview of studies investigating the use of PCT in different types and sites of infection

Type of infection	Study designs	PCT cut-off (ug/L)	Benefit of using PCT?	Main conclusions	Selected References
Abdominal Infections	observational	0.25	?	PCT may help to exclude ischemia and necrosis in bowel obstruction	[29-32]
Arthritis	observational	0.1-0.25	+	PCT differentiates non-infectious (gout) arthritis from true infection	[37,38,73]
Bacteremic infections	observational	0.25	++	Low PCT levels help to rule out bacteremic infections	[14,15,74]
Blood stream infection (primary)	observational	0.1	++	PCT differentiates contamination from true infection	[13]
Bronchitis	RCT	0.1-0. 5	+++	PCT reduces antibiotic exposure in the ED without adverse outcomes	[50,52]
COPD exacerbation	RCT	0.1-0. 5	+++	PCT reduces antibiotic exposure in the ED and hospital without adverse outcomes	[50-52]
Endocarditis	observational	2.3	+	PCT is an independent predictor for acute endocarditis with high diagnostic accuracy	[27,28]
Meningitis	before-after	0.5	+	PCT reduces antibiotic exposure during outbreak of viral meningitis	[75-77]
Neutropenia	observational	0.1-0.5	+	PCT is helpful at identifying neutropenic patients with systemic bacterial infection	[39-41]
Pancreatitis	observational	0.25-0.5	?	PCT correlates with severity and extend of infected pancreatitis	[33,36]
Pneumonia	RCT	0.1-0. 5; 80-90% ↓	+++	PCT reduces antibiotic exposure in the hospital without adverse outcomes	[16,50,52-55]
Postoperative fever	observational	0.1-0.5	+	PCT differentiates non-infectious fever from post-operative infections	[78]
Postoperative Infections	RCT	0.5-1.0; 75-85% ↓	++	PCT reduces antibiotic exposure in the surgical ICU without adverse outcomes	[64,65]
Severe sepsis/Shock	RCT	0.25-0.5; 80-90% ↓	+++	PCT reduces antibiotic exposure in the ICU without adverse outcomes	[61,62]
Upper respiratory tract infections	RCT	0.1-0.25	++	PCT reduces antibiotic exposure in primary care without adverse outcomes	[58]
Urinary tract infections	observational	0.25	+	PCT correlates with severity of urinary tract infections	[15,26]
Ventilator-associated pneumonia	RCT	0.1-0.25	++	PCT reduces antibiotic exposure without adverse outcomes	[62,63]

Abbreviations: COPD, chronic obstructive pulmonary disease; ED, Emergency department; PCT, procalcitonin; RCT, randomized-controlled trial. The level of evidence in favor or against PCT for each infection was rated by two of the coauthors (PS, WCA) independently and disagreements were resolved by consensus. + moderate evidence in favor of PCT; ++ good evidence in favor of PCT; +++ strong evidence in favor of PCT; ? evidence in favor or against the use of PCT still undefined

PCT demonstrated a better discriminatory ability compared to WBC and CRP [13]. At a cut-off of 0.1 ug/L, PCT had a very high sensitivity to exclude true infection. Two other studies, focused on the use of PCT to predict bacteremia infections in patients with CAP [14] and urinary tract infections (UTI) [15]. A PCT cut off of 0.25 ug/L was most helpful to exclude bacteremic disease with a high negative predictive value in both settings.

In UTIs, evidence for the utility of PCT comes primarily from the pediatric literature, where it has a similar sensitivity but superior specificity compared to CRP for the prediction of pyelonephritis in children with febrile UTIs [26]. It correlates with the extent of renal involvement and with renal scarring. Similarly, in patients with infectious endocarditis, circulating PCT levels were elevated compared to non-infected patients in two independent studies [27,28]. Unfortunately, a reliable PCT threshold for diagnosing or excluding infective endocarditis was neither proposed nor tested in intervention studies. Importantly, subacute forms of endocarditis or prosthetic-valve endocarditis may show different characteristics compared to acute forms due to their low inflammatory nature and possibly biofilm production.

Few studies have investigated the use of PCT in intra-abdominal infections [29-36]. While PCT showed promise as a marker to exclude perforation and ischemia in obstructive bowel syndrome [32], the utility in acute appendicitis [31] and pancreatitis [33,36] was limited and PCT was more helpful as a prognostic marker for severe disease and adverse outcome. While localized infections may not induce a massive PCT up-regulation, studies found PCT of diagnostic utility in patients with

arthritis [37] and osteomyelitis [38], particularly when subtle increases and a low PCT cut off (0.1 ug/L) were considered.

Different studies have evaluated the utility of PCT in patients with febrile neutropenia [39-41]. A recent systematic review found 30 articles on the topic and concluded that PCT has value as a diagnostic and prognostic tool in patients with febrile neutropenia, but that due to differences in patient populations and study qualities, further research is needed [40]. Importantly in this regard, the production of PCT seems not to be attenuated by corticosteroids [42,43] and PCT production does not rely on white blood cells [44-46]. A study including 102 critically ill patients with systemic infections in a medical intensive care unit (ICU) found significantly lower CRP and IL-6 levels, but similar PCT levels, in patients treated with systemic corticosteroids (20 to 1500 mg/day of prednisone parenterally) compared to untreated patients[42]. These observations were confirmed in healthy male volunteers who received different doses of prednisolone up to 30 mg before a sepsis-like syndrome was induced with *Escherichia coli* lipopolysaccharide (LPS) injections[43]. While other biomarkers were significantly inhibited in a dose-dependent way, levels of PCT showed no inhibition within the study period. Whether this is also true for other corticosteroid doses, however, remains unknown. The value of PCT in febrile neutropenia may be as part of a combination with other biomarkers of bacterial infection such as IL-6 and IL-8 as shown in a small study of pediatric patients with febrile neutropenia [39].

Procalcitonin as a guide for antibiotic decisions: results from randomized-controlled studies

The clinical implications of the above mentioned observational studies may be limited by differences in disease definitions and patient groups, use of insensitive (semi-quantitative) PCT assays, and different methodological issues such as observer bias, selection bias and issues of sample availability, co-infection and colonization. To overcome these limitations, several randomized-controlled studies have investigated the use of PCT to assist in decisions about initiation and/or duration of antibiotic therapy (antibiotic stewardship). Thereby the benefit of PCT was measured by clinical outcomes, assuming that if the patient recovers without antibiotics, there was no relevant bacterial illness in need of antibiotic therapy. Importantly, all intervention studies used fully automated highly sensitive PCT assays, the results of which can be obtained in the clinical routine of an emergency department within one hour thus permitting bed-side decision making. Recently, different options for PCT testing have become available, including the KRYPTOR [25], the VIDAS system (Biomerieux) [47], the Liaison BRAHMS PCT (DiaSorin)[48] and the Elecsys BRAHMS PCT (Roche Diagnostics) [49].

All published studies on antibiotic stewardship used similar clinical algorithms with recommendations for or against antibiotic treatment based on PCT cut-off ranges. For moderate risk patients with respiratory tract infections in the emergency department (Figure 2), algorithms recommended initiation and discontinuation of antibiotic therapy based on four different cut-off ranges. Initial antibiotics were withheld mostly in patients with low risk for systemic infection with acute bronchitis or exacerbation of chronic obstructive pulmonary disease [ECOPD]). Clinical re-evaluation and a repeated measurement of PCT were recommended after 6 to 24 hours if the clinical condition did not improve spontaneously. If PCT values were increased and antibiotic therapy was initiated, repeated PCT measurements were recommended every one to two days, depending on the clinical severity of disease, and antibiotics were discontinued using the same cut off ranges or a marked drop by 80% to 90% if initial levels were high (for example >5 μg/l). To assure safety, specific criteria were predefined where this algorithm could be overruled, such as life-threatening disease or immediate need for ICU admission. For high risk patients in the ICU setting (Figure 3), algorithms focused on discontinuation of antibiotic therapy if a patient showed a clinical recovery and PCT levels decreased to 'normal' levels, or by at least 80% to 90%.

The first intervention study testing PCT as a guide for antibiotic decisions included patients with different types and severities of respiratory infections [50]. Clinical outcomes for both groups were similar, but the PCT-guided group had markedly lower rates of antibiotic prescriptions (44% versus 83%), particularly in patients with ECOPD and acute bronchitis. Two subsequent trials evaluated the effect of PCT guidance for antibiotic discontinuation in CAP and ECOPD. PCT guidance reduced the duration of antibiotic therapy by 65% in CAP patients [16] and the prescription of antibiotics from 72% to 40% in ECOPD patients [51]. A subsequent multicenter trial [52] confirmed earlier results and found a reduction of antibiotics by 32% in CAP, by 50% in ECOPD and by 65% in acute bronchitis. Again, antibiotic exposure in ECOPD and acute bronchitis decreased mainly by not initiating treatment at all, whereas for CAP it was principally from reduction in duration of therapy. Importantly, the overall rate of adverse events was similar in both study arms and excluded a risk of more than 0.4% for PCT guided patients. Interestingly, patients with bacteremia CAP had markedly increased PCT concentrations resulting in longer treatment duration compared to culture-negative CAP patients with a lower infection-related risk [17].

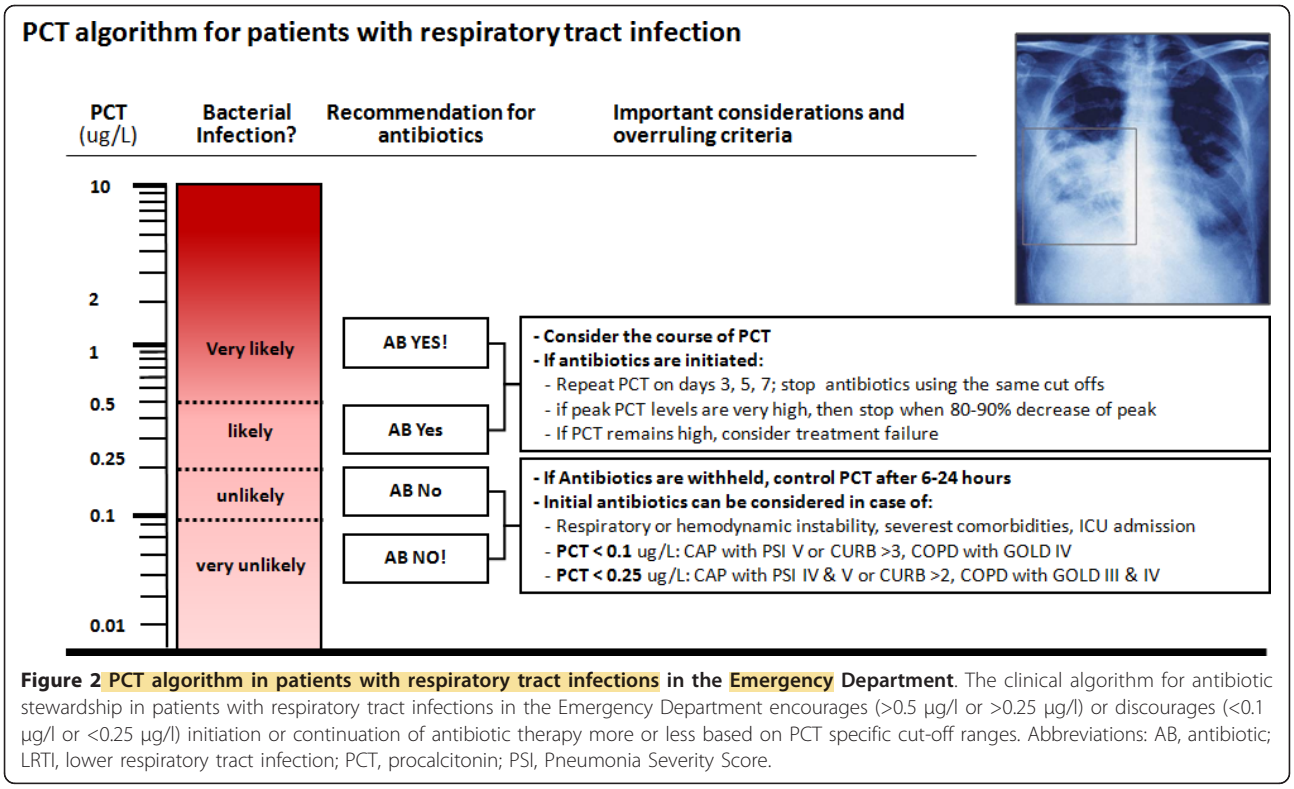

Figure 2 PCT algorithm in patients with respiratory tract infections in the Emergency Department. The clinical algorithm for antibiotic stewardship in patients with respiratory tract infections in the Emergency Department encourages (>0.5 μg/l or >0.25 μg/l) or discourages (<0.1 μg/l or <0.25 μg/l) initiation or continuation of antibiotic therapy more or less based on PCT specific cut-off ranges. Abbreviations: AB, antibiotic; LRTI, lower respiratory tract infection; PCT, procalcitonin; PSI, Pneumonia Severity Score.

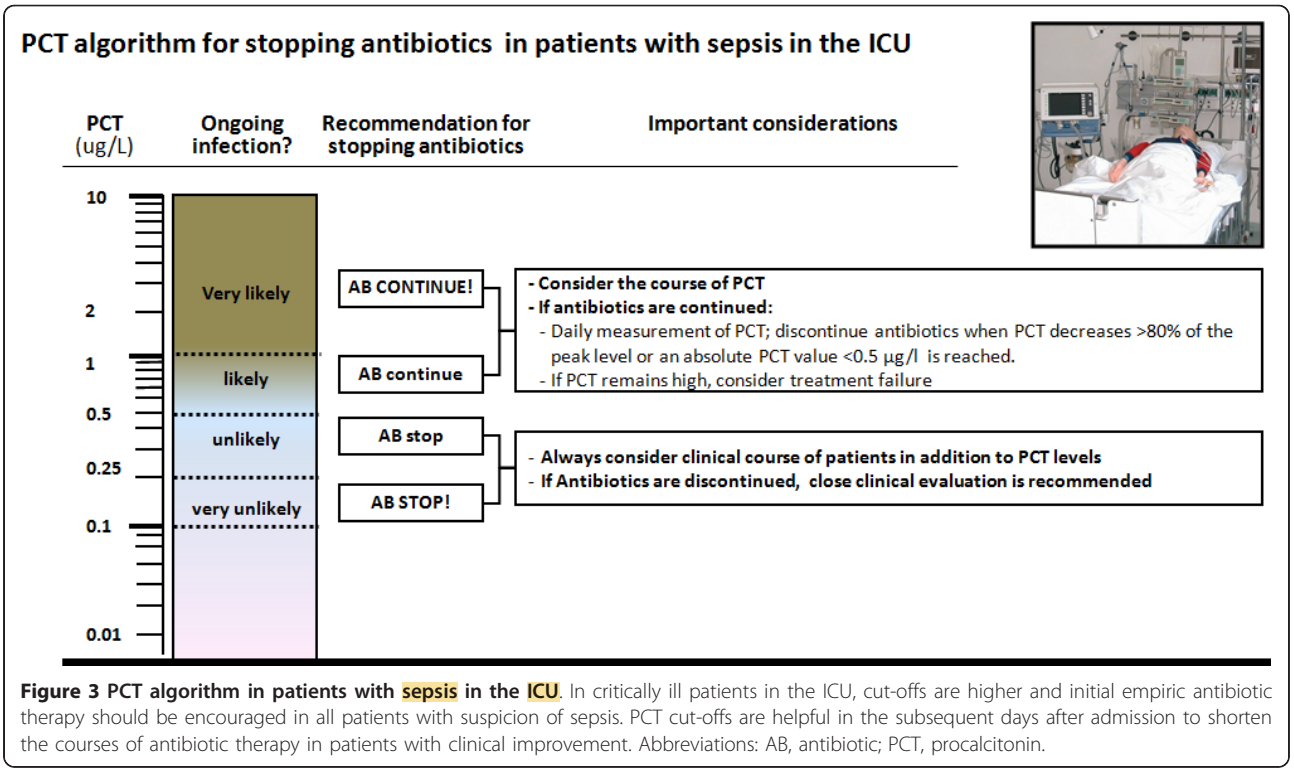

Figure 3 PCT algorithm in patients with sepsis in the ICU. In critically ill patients in the ICU, cut-offs are higher and initial empiric antibiotic therapy should be encouraged in all patients with suspicion of sepsis. PCT cut-offs are helpful in the subsequent days after admission to shorten the courses of antibiotic therapy in patients with clinical improvement. Abbreviations: AB, antibiotic; PCT, procalcitonin.

Similar results in patients with respiratory infections were also reported in trials from Denmark [53] and China [54,55], and recently from an observational 'real life'- quality control survey in Switzerland [56].

Arguably, the most important (over-) use of antibiotics occurs in primary care. As many as 75% of patients with upper and lower respiratory infections receive antibiotics, despite the mostly viral origin of the condition [57]. Two multicenter primary care trials, powered for non-inferiority of clinical outcomes, investigated the safety and feasibility of PCT guided algorithms in patients with upper and lower respiratory infections, essentially relying on an initial PCT measurement only [58-60]. Both trials found substantial reductions in antibiotic exposure (by 75% and 42%), and similar clinical outcomes, particularly a similar time to recovery.

In more high risk patients in the ICU setting, different trials have investigated the use of PCT, mainly for discontinuation of antibiotics. The first small proof of concept study [61] found a four-day reduction in the duration of antibiotic therapy in patients with severe sepsis, but only in the per protocol analysis. A subsequent large multicenter trial in France recently validated this concept in more than 600 patients [62]. PCT guided patients had similar 30-day mortality rates and similar rates of relapses, but markedly more antibiotic-free days alive (14.3 versus 11.6). Another multinational ICU study focused on ventilator-associated pneumonia and found that PCT guidance resulted in a higher number of antibiotic free-days alive (13 versus 9.5 days) [63]. Two German studies assessed the effect of PCT guidance in surgical ICU patients with suspected bacterial infections in the post-operative course [64,65]. PCT guidance resulted in a significant reduction of antibiotic therapy and similar medical outcomes. In addition, the length of intensive care treatment in the PCT-guided group was significantly shorter than that in the control group (15.5 versus 17.7 days), a finding similar to the first ICU study [61]. Importantly, the use of PCT for discontinuation of antibiotics in ICU patients is still limited by a relatively small number of patients included in previous trials and awaits further large-scale validation. There are currently different ongoing trials focusing on this vulnerable patient population that should shed further light on the benefits and harms of PCT use in ICU patients.

Limitations and areas of uncertainty

Sepsis is not a well-defined disease, but a consequence of different infectious disease entities and far too complex to be reduced to a single cut-off of any surrogate marker. Limitations of every PCT measurement include false-positive and false-negative results [8,11]. Different pathogens might induce distinct responses resulting in a variable up-regulation of circulating PCT levels [66]. While highly elevated PCT levels were found in patients with pneumococcal CAP [14], the same was not true in CAP due to atypical organisms such as mycoplasma [66]. Antimicrobial pre-treatment may influence the level of PCT resulting in lower PCT levels [67], although it remains unclear whether this relates to a direct effect or rather to lower microbial burden in patients treated with antibiotics. Unspecific elevations of PCT levels in the absence of a bacterial infection can typically be seen in situations of massive stress, for example after severe trauma and surgery [8,68-70] or in patients after cardiac shock [71]. Although the available evidence from intervention studies favors the use of PCT for de-escalation of antibiotic therapy, the same may not be true for escalation of antibiotics when PCT increases as recently demonstrated [72]. In this study PCT-guided escalation of diagnostic procedures and antibiotic therapy in the ICU did not improve survival and led to worse secondary outcomes in patients.

Summary, future directions and conclusions

For upper and lower respiratory tract infection in ICU patients with sepsis and post-operative infections, randomized-controlled studies have shown the efficacy of using PCT algorithms to guide antibiotic decisions. For other types of infections, only observational studies are available which are importantly limited by the lack of a true gold standard. Most intervention studies were conducted in European countries including Switzerland, Germany, France and Denmark (and two in China) and validation in other countries and continents is therefore warranted. Importantly, PCT levels must always be evaluated in the context of a careful clinical and microbiological assessment. As the kinetics of PCT are of particular diagnostic and prognostic interest, repeated measurements should be performed if feasible, especially in persistently sick patients if antibiotics are withheld. The limitations of every PCT measurement include false-positive and false-negative results [8]. Unspecific elevations of PCT levels in the absence of a bacterial infection can typically be seen in situations of massive cell death, for example after severe trauma or surgery [8,68,69]. In these situations, PCT values are usually only moderately elevated and show a rapid decline in follow-up measurements. Conversely, falsely low PCT levels, typically seen during the early course or localized state of an infection, often show an increase in the follow-up measurements. Therefore, highly sensitive PCT assays are required, as subtle changes of PCT at very low concentrations can be monitored, increasing the sensitivity of the test and thus the safety of patients.

Emerging bacterial resistance to antimicrobial agents calls for more effective efforts to reduce the unnecessary

and prolonged use of antibiotics in self-limiting non-bacterial and resolving diseases [1]. Patients and physicians share a common goal of improving symptoms from infection as fast as possible and often see antibiotics as the most expeditious intervention to achieve it. This one-size fits-all approach fails to consider the basic questions of who benefits from antibiotic therapy, and if treated, what would be the optimal duration. Using PCT, which mirrors the likelihood of bacterial infection and the severity of infection, to guide antibiotic therapy, is a persuasive, evidence-based approach to a more rational use of antibiotics.

List of abbreviations

AB: antibiotic; CAP: community-acquired pneumonia; CRP: C-reactive protein; ECOPD: exacerbation of chronic obstructive pulmonary disease; ED: Emergency department; ICU: intensive care unit; IFN: interferon; IL: interleukin; LPS: lipopolysaccharide; PCT: procalcitonin; TNF: tumor necrosis factor; RCT: randomised-controlled trial; UTI: urinary tract infection; WBC: white blood cells.

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Authors' contributions

PS drafted the initial manuscript. WCA and BM commented on the manuscript. All authors approved the final version.

Competing interests

Drs Schuetz, Albrich, and Mueller reported receiving support from BRAHMS Inc and Biomerieux to attend meetings and fulfill speaking engagements. Dr Mueller reported serving as a consultant and receiving research support from BRAHMS and BioMérieux Inc.

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