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Review

# Procalcitonin: Between evidence and critical issues

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ABSTRACT

Sepsis is a life-threatening organ dysfunction caused by a dysregulated response of the host to infection. It represents one of the major health care problems worldwide. Unfortunately, the diagnosis of sepsis is challenging for many reasons, including a lack of a sufficiently sensitive and specific diagnostic test. When procalcitonin (PCT) was discovered, it was thought that it could become the best test for identifying patients with sepsis. From the evidence sources in the available literature, it is now clear that the power of PCT in differentiating infectious from non-infectious forms of systemic inflammatory response syndrome in adults, and in stratifying morbidity and mortality risk, is limited. Nevertheless, PCT determination can be a useful tool for diagnosing late-onset neonatal sepsis, bacterial meningitis and other forms of organ-related bacterial infections and, above all, it can be used for guiding antibiotic stewardship in critical patients. The real impact of this application of PCT testing, however, still needs to be clearly defined. Laboratories should offer unrestricted PCT testing only to intensive care units (as an aid in decision for continuing or stopping antibiotics) and pediatric wards. For all other clinical wards, the laboratory should guide PCT requests and give them support towards the most appropriate approach to testing.

## 1. Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated response of the host to systemic infection [1]. Septic shock is the most severe subset of sepsis, with significantly increased mortality, caused by profound underlying circulatory and cellular metabolism abnormalities [1]. Both sepsis and septic shock are major health care problems, affecting 20 to 30 million people every year worldwide, with mortality ranging from < 10% to > 60% with increasing disease severity [2].

The effect of sepsis treatment is extremely time dependent. Survival chance of patients is maximized if antibiotics are administered within 1 h from clinical presentation and each hour of delay in antibiotic administration results in a significant increase of mortality for septic shock [3]. Unfortunately, in most cases it is difficult to clinically distinguish between a patient with organ dysfunction caused by an infection, which would benefit from early antibiotic treatment, and a patient suffering from a systemic inflammatory response syndrome (SIRS) due to other causes. The standard diagnostic tool available today for bacterial sepsis is blood culture, which unfortunately needs hours to deliver results and, importantly, is inconclusive in ~40% of cases [4]. On the other hand, it is necessary to find a balance between aggressive and precocious antibiotics administration to all patients suspected of having sepsis and the possible harm associated with unnecessary antibiotic treatment, in terms of drug toxicity and bacterial resistance [5]. Consequently, over the years, there has been a urgent need to find a sufficiently sensible and specific laboratory biomarker, which could allow distinguishing between a non-infectious SIRS and sepsis. One of these biomarkers is undoubtedly procalcitonin (PCT). Because its use as a clinical biomarker has many critical and unsolved issues, in this review we aim to highlight and discuss the main results available from scientific evidence produced in the 25 years passed since its discovery.

## 2. Biochemical and biological aspects of PCT

PCT is a member of the calcitonin gene-related peptide-amylin-procalcitonin-adrenomedullin family. It is composed of 116 amino acids (MW, 14 kDa) and is the precursor of the hormone calcitonin [6]. The PCT gene (*CALC-1*) is located on chromosome 11 and codes for a pre-prohormone of 141 amino acids composed by an initial signaling sequence of 25 amino acids, which is degraded immediately after protein translation. The PCT sequence includes the PCT amino-terminal region, the calcitonin region and a carboxy-terminal region called katacalcin. In normal conditions, *CALC-1* is expressed almost exclusively by

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neuroendocrine thyroid C cells and produced PCT is stored in the Golgi apparatus, justifying the very low concentrations found into the blood stream. During systemic infections, *CALC-1* is up-regulated and consequently expressed in all cells of the organism, leading to the release of elevated amounts of PCT in the circulation [7]. Many inflammatory cytokines contribute to the up-regulation of *CALC-1*, except for interferon-γ, which reduces *CALC-1* expression, therefore resulting in the lower PCT concentrations found in viral infections.

PCT has a half-life of ~22–29 h and, during bacterial infections, its levels start to rise 4 h after onset and reach the peak between 12 and 24 h, earlier than C-reactive protein (CRP), which peaks after 2–3 days [4]. It is important to note that PCT concentrations are significantly raised in newborns during the first three days of life, with concentrations normalizing to those of adults in the subsequent days [8]. Furthermore, PCT can be raised in other conditions such as multiple trauma, medullar thyroid cancer and heatstroke [9–11]. Barassi et al. studied the biological variability of PCT, estimating an intra-individual CV of 16% and inter-individual CV of 22% [12]. As expected from its metabolic regulation, the analyte has a relatively high inter-individual variability, with a low index of individuality, which implicates that the use of population-based reference intervals or decision limits to interpret single PCT results may be inadequate [13]. Results can be better interpreted by performing serial measurements in the subject to detect concentration changes higher than the reference change value, which represents the variation needed between two serial results from the same individual to be significantly different [13].

## 3. PCT in the diagnosis of bacterial infections

### 3.1. Bacteremia and sepsis in adults

Over the years, a great amount of observational studies has been carried out in order to determine the diagnostic accuracy of PCT as a marker of bacteremia and sepsis in adults. However, the absence of an efficient diagnostic gold standard to which compare results, the subject selection bias, the lack of agreement on optimal cut-off values, the heterogeneity of enrolled populations, and the lack of standardization of PCT assays all contribute to the conflicting and confusing results of these studies [14]. Many authors have tried to obtain results of improved statistical power by producing meta-analyses [15–24]. As can be noticed from Table 1, all meta-analyses gave fundamentally similar results. The diagnostic accuracy of PCT, represented by the areas under the summary receiver operating characteristic curves (SROC-AUC), never reached 90%, except for the study by Ren et al. [20], which includes only a very specific subgroup of adult patients (burn victims) and which results were not confirmed by the similar meta-analysis conducted later by Cabral et al. [22]. Pooled sensitivities and specificities did not surpass 80% and both positive and negative likelihood ratios, when available, showed a small to moderate impact of PCT results on clinical decision making. It is curious to note that, despite quite similar results, conclusions of different investigators were contrasting, showing a possible bias on the data interpretation. Most meta-analyses of diagnostic accuracy studies presented positive conclusions and a majority contained a form of overinterpretation. As nicely underlined by McGrath et al. [25], this may lead to unjustified optimism about test performance and erroneous clinical decisions and recommendations. Overall, these data show a moderate diagnostic performance of a single PCT measurement for the identification of patients suffering of bacteremia and sepsis, both in mixed populations and in specific subsets, such as those of intensive care units (ICU) or emergency departments (ED).

### 3.2. Sepsis in newborns

PCT seems to have a similar performance for diagnosing sepsis in newborns. A meta-analysis by Vouloumanou et al. [26], including 16 studies for a total of 1959 patients, found pooled sensitivity and specificity of 81% [95% confidence interval (CI): 74–87%] and 79% (69–87%), respectively, with a SROC-AUC of 0.87 (95% CI: 0.84–0.90) and pooled positive and negative likelihood ratios of 3.9 (95% CI: 2.5–6.0) and 0.24 (0.17–0.34), respectively. As PCT values are physiologically increased during the first 72 h of life both in preterm and term neonates [27,28], and this may complicate the marker interpretation, the authors further analyzed the retrieved studies by separating them in the two subgroups for early-onset (within 72 h from birth) and late-onset neonatal sepsis. Five studies (535 patients) were included in the analysis of PCT diagnostic accuracy for late-onset sepsis. The pooled sensitivity of PCT for this group (90%; 95% CI: 73–97%) was significantly higher than for the early-onset group (76%; 95% CI: 68–82%) and so was the specificity, which was 88% (95% CI: 72–96%) for the late-onset group and 76% (60–87%) for the early-onset group. The SROC-AUC was 0.95 (0.93–0.97) in the late-onset group and only 0.78 (0.74–0.81) in the early-onset group. Positive and negative likelihood ratios were 7.7 (3.1–18.9) and 0.11 (0.04–0.31) in the late-onset group and 3.2 (1.8–5.7) and 0.32 (0.23–0.43) in the early-onset group, respectively. Therefore, the diagnostic accuracy of PCT seems higher for neonates with late-onset (> 72 h of life) sepsis than for those with early-onset sepsis, even though the limited number of available studies does not allow a firm conclusion. Regarding this topic, Chiesa et al. [29] have pointed out the need of higher quality studies to provide more

**Table 1**
Data from published meta-analyses evaluating the diagnostic accuracy of procalcitonin for bacteremia and sepsis.

| Authors, year [ref] | No. of studies | No. of subjects | Type of patients | AUC (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) | +LR (95% CI) | -LR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Uzzan et al[a], 2006 [15] | 25 | 2699 | ICU | – | – | – | – | – |
| Jones et al., 2007 [16] | 17 | 2008 | ED | 0.84 (0.75–0.90) | 0.76 (0.66–0.84) | 0.70 (0.60–0.79) | – | – |
| Tang et al., 2007 [17] | 14 | 1602 | ICU | 0.79 | 0.73 (0.69–0.77) | 0.71 (0.67–0.76) | 3.03 (2.51–3.65) | 0.43 (0.37–0.48) |
| Wacker et al., 2013 [18] | 30 | 3244 | ICU | 0.85 (0.81–0.88) | 0.77 (0.72–0.81) | 0.79 (0.74–0.84) | 4.00 | 0.29 |
| Hoeboer et al., 2015 [19] | 58 | 16,514 | Mixed | 0.79 | 0.76 (0.72–0.80) | 0.69 (0.64–0.72) | – | – |
| Ren et al., 2015 [20] | 8 | 566 | Burned patients | 0.92 | 0.74 (0.68–0.79) | 0.88 (0.84–0.92) | 5.75 (3.79–8.72) | 0.33 (0.15–0.77) |
| Liu et al., 2016 [21] | 59 | 7376 | Mixed | 0.85 (0.82–0.88) | 0.79 (0.75–0.83) | 0.78 (0.74–0.81) | – | – |
| Cabral et al., 2016 [22] | 14 | – | Burned patients | 0.83 (0.76–0.90) | 0.77 (0.72–0.80) | 0.65 (0.62–0.69) | – | – |
| Wu et al., 2017 [23] | 13 | 2915 | Mixed | 0.86 (0.82–0.88) | 0.78 (0.72–0.83) | 0.79 (0.73–0.85) | – | – |
| Tan et al., 2019 [24] | 9 | 1368 | Mixed | 0.85 (0.82–0.88) | 0.80 (0.69–0.87) | 0.77 (0.60–0.88) | 3.42 (1.79–6.52) | 0.27 (0.16–0.45) |

AUC: area under the summary receiver operating characteristic (SROC) curve; CI: confidence interval; +LR: positive likelihood ratio, −LR: negative likelihood ratio; ICU: intensive care unit; ED: emergency department.

[a] Uzzan et al. only reported the diagnostic odds ratio: 15.7, 95% CI: 9.1–27.1.

reliable information for guiding decisions on the use and interpretation of PCT test results in the management of septic neonates. Particularly, this is true in newborns with early-onset sepsis, since it remains unclear how to interpret PCT concentrations in the first 72 h of life. Features which appear to have a possible biasing effect in the available studies are the way to select the target population and to recruit eligible subjects, the description of the reference standard for diagnosis (or exclusion) of neonatal sepsis and its rationale, and of the study population in which tests were executed (study period, clinical and demographic features, distribution of illness severity scores, etc.) [29].

### 3.3. Bacterial meningitis

Like sepsis, a prompt differentiation between bacterial and non-bacterial origin of acute meningitis is critical in order to initiate an adequate therapy as soon as possible and reduce the high risk of morbidity and mortality associated with the condition. However, as for sepsis and non-infectious SIRS, the two forms of acute meningitis share many clinical features, making the differential diagnosis quite challenging [30]. At present, the diagnostic standard for bacterial meningitis is a combination of clinical features and laboratory tests done both on serum (including CRP) and on cerebrospinal fluid. However, these tests are characterized by inadequate sensitivity and specificity. Therefore, studies were performed to investigate the ability of PCT in distinguishing between acute bacterial and non-bacterial meningitis. These studies have been included in two recent meta-analyses. Vikse et al. [31] analyzed 9 primary studies including 725 adult patients, while Wei et al. [32] analyzed 22 studies for a total of 2058 patients, including 8 studies which enrolled pediatric populations. Results of the two meta-analyses are summarized in Table 2. Overall, PCT seems to have an excellent power in differentiating bacterial meningitis from other forms of meningeal inflammation, as suggested by the SROC-AUCs close to 1.00. In particular, the marker seems to be more specific than sensitive.

### 3.4. Prediction of renal parenchymal involvement in children with urinary tract infections

An interesting, even though little known, application of PCT is for differentiating acute pyelonephritis from lower urinary tract infections (UTIs) in children. A meta-analysis by Mantadakis et al. [33] reviewed 10 studies, comprehensive of 627 patients. By excluding two low quality studies, the odds ratio (OR) of positive PCT ($> 0.5\,\mu g/L$, measured at presentation) to detect renal parenchymal involvement was 26.7 (95% CI: 10.3–69.4). These data showed that PCT has a satisfactory accuracy for predicting renal parenchymal involvement in children with UTIs. This is of interest because it could reduce the number of expensive, cumbersome and irradiating procedures needed to demonstrate renal parenchymal involvement or to asses the progression of renal damage in children with UTIs.

A quite recent study has shown that a multi-marker approach, using PCT, urinalysis and blood neutrophil count, has the potential to rule out serious bacterial infections, including UTIs, bacteremia, and meningitis, in febrile infants $\leq 60$ days old, with a very high negative predictive value [99.6% (95% CI: 98.4–99.9)] [34]. However, these data need to be further validated.

## 4. PCT for prognostic evaluation of septic patients

The prognostic power of PCT has been evaluated mainly in adult patients with sepsis. However, as in the case of the use of PCT for diagnosing sepsis, the existing evidence does not support the PCT value as a single marker for assessing patient prognosis, even though the measurement may be useful in association with other clinical features. Arora et al. [35] reported significantly lower concentrations of PCT in surviving vs. non-surviving patients with sepsis but did not present any data about the power of PCT for predicting mortality. A meta-analysis by Liu et al. [36] reported a SROC-AUC of 0.77 (95% CI: 0.73–0.80), with sensitivity and specificity of 0.76 (0.67–0.82) and 0.64 (0.52–0.74), respectively, for mortality prediction with a single PCT measurement, which describe an overall low prognostic power of the marker. More promising results were obtained by Schuetz et al. [37], who found a significantly higher 28-day all-cause mortality (hazard ratio: 2.05; 95% CI: 1.30–3.24) in severe sepsis patients that had a decrease in PCT values of $< 80\%$ between baseline and day 4 of treatment.

## 5. PCT for antibiotic stewardship

After it became clear that PCT could not be used as a single marker to diagnose sepsis or to predict mortality risk in critically ill patients, the focus shifted towards its use as a marker to guide initiation and termination of antibiotic therapies in those patients [14,38]. Major problems of prolonged antibiotic treatments in patients with severe bacterial infections are undoubtedly the risk to develop microbial resistances and drug toxicity effects. Antibiotics should be administered only to patients with true bacterial infectious processes and stopped as soon as the infection is under control, hence reducing the length of drug exposure, with consequent positive effects for the patient and decreasing costs for the institution [5].

In 2004, Christ-Crain et al. [39] published the first trial looking at the effect of PCT-guided treatment on antibiotic use. The study showed that antibiotic administration based on PCT concentrations leads to a significant reduction in prescribed antibiotics, duration of treatment, antibiotic costs per patient, and antibiotic use per 1000 days of follow-up. Quite recently, Schuetz et al. reviewed the existing literature and found that results from 26 trials were available about the effect of PCT-guided treatment in acute upper and lower respiratory tract infections (RTIs), accounting for 6708 patients over 12 different countries [40]. Of these trials, 13 were conducted in ICU, 11 in ED and two in primary care settings. In the meta-analysis, PCT-guided antibiotic therapy was found to be significantly correlated to a reduction in antibiotic prescriptions (adjusted OR: 0.27, 95% CI: 0.24–0.32), in antibiotic-associated adverse effects (adjusted OR: 0.68, 95% CI: 0.57–0.82) and to duration of antibiotic therapy (difference in days: -1.83, 95% CI: $-2.15$ to $-1.5$). Moreover, PCT-guided therapy was proven safe since no increases were observed in length of hospital stay and the 30-day mortality of patients was slightly reduced in the PCT group. The data of this meta-analysis were reported in the 2017 version of the Cochrane review titled “Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections” [41] and in a clinical evidence synopsis published on the Journal of the American Medical Association [42]. It is noteworthy that the Cochrane Library declared that the first author will step down as lead author at the update of the review because of

**Table 2**
Data from published meta-analyses evaluating the diagnostic accuracy of procalcitonin for bacterial meningitis.

| Authors, year [ref] | AUC (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) | +LR (95% CI) | -LR (95% CI) |
|---|---|---|---|---|---|
| Vikse et al., 2015 [31] | 0.97 (0.94–0.99) | 0.90 (0.84–0.94) | 0.98 (0.97–0.99) | 27.3 (8.2–91.1) | 0.13 (0.07–0.26) |
| Wei et al., 2016 [32] | 0.98 (0.97–0.99) | 0.95 (0.89–0.97) | 0.97 (0.89–0.99) | 31.7 (8.0–124.8) | 0.06 (0.03–0.11) |

AUC: area under the summary receiver operating characteristic (SROC) curve; CI: confidence interval; +LR: positive likelihood ratio, −LR: negative likelihood ratio.

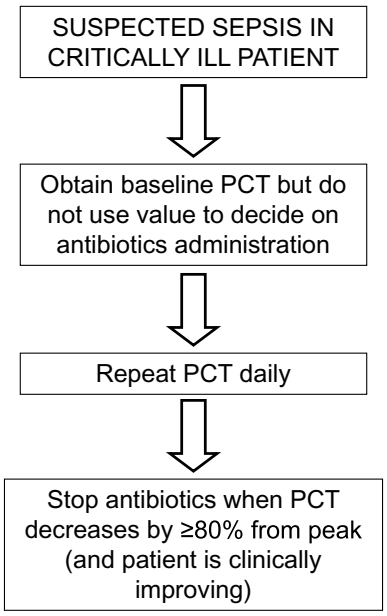


**Fig. 1.** Example of procalcitonin (PCT)-guided algorithm for antibiotic stewardship in critically ill patients used in the authors' institution.

conflicts of interest breaching the Cochrane's commercial sponsorship policy.

Although substantial evidence suggests that PCT-guided antibiotic stewardship is effective, there is one important limitation: most of the published trials have been conducted primarily in Europe (mainly Switzerland) and China, often by the same groups; conclusions cannot therefore be extended to other populations worldwide where antibiotic administration approaches may significantly differ. This issue was pointed out in 2016 guidelines of the Infectious Diseases Society of America (IDSA) on implementing antibiotic stewardship programs [43]. The guidelines suggest the use of serial PCT measurements to help decrease antibiotic use in ICU but underline that the strength of recommendation for the United States (US) institutions is weak and supported by moderate quality evidence.

Another limitation of studies on PCT-guided antibiotic therapy is represented by the strictly controlled conditions under which trials were performed, opposed to the situations seen in “real life”. One study was done in 2012 with the scope to validate PCT-guided antibiotic treatment in lower RTIs in real-life conditions [44]. Results showed that a PCT algorithm may effectively reduce antibiotic use without increasing the risk of complications. However, once again, this study had some important limitations, such as its observational design, the fact that the great majority of participating centers (10 out of 14) were in Switzerland and only one in the US (in which the compliance with PCT algorithm was only 35%) and the testing costs were high. It seems extremely difficult to predict the level of adherence to PCT-guided antibiotic stewardship outside of the strict setting of controlled trials, since in “real life” settings it is impossible, and maybe unethical, to eliminate the subjective clinical evaluation of physicians when important therapeutic decisions need to be made.

Regarding the primary care setting, where the most important overuse of antibiotics for acute upper RTIs occurs, only two small trials were performed [45,46]. Both studies found that PCT-guided therapy in patients with RTIs was associated with a significant reduction in antibiotic prescription. An individual patient data meta-analysis done using results from these two studies showed that the main effect of PCT testing was in reducing antibiotic use, with a decrease of overall antibiotic exposure of 2.4 days [47]. However, subgroup analysis did not confirm the effectiveness of the approach in patients with acute tonsillitis, acute laryngitis or tracheitis, which represent the prevalent causes of RTIs in primary care. Finally, yet importantly, advantages on CRP were not shown. Since primary care is probably the setting in which antibiotics are most likely misused, more efforts are warranted to produce robust evidence that PCT guidance on antimicrobial therapy works in this setting.

As for newborns with suspected early-onset sepsis, Stocker et al. [8] recently found that PCT-guided decision making was superior to standard care in reducing the duration of the antibiotic treatment. However, the safety of the application of the PCT algorithm could not be determined because of the low occurrence of complications.

### 5.1. PCT-guided algorithms for antibiotic stewardship

As discussed above, because of the relatively high inter-individual biological variability of PCT [12], fixed cut-off values may not be the best option for interpreting PCT results. If used, cut-offs should however be adapted to the specific clinical setting. For instance, in ED patients with lower RTIs, PCT values $< 0.1\,\mu g/L$ indicate bacterial etiology as very unlikely, while values $> 0.5\,\mu g/L$ indicate a high probability for this etiology and strongly support antibiotics initiation [48]. In ICU, the same information is obtained with PCT values $< 0.25\,\mu g/L$ and $\geq 1.0\,\mu g/L$, respectively [49].

The inherent PCT's “disadvantage” of displaying high individuality should be circumvented by serial biomarker measurements. Algorithms proposed for PCT-guided antibiotic stewardship should employ PCT measurements every 24–48 h, considering the biomarker's half-life, with stopping of antibiotics if a significant decrease of serum PCT concentrations from peak value is obtained (Fig. 1). An example of an algorithm of this kind is the one proposed by the authors of the PRORATA trial [49]. This algorithm, which is probably the most known and adopted worldwide, encourages stopping of antibiotic administration in septic ICU patients if PCT decreases by $\geq 80\%$ from peak concentration.

## 6. PCT cost: A stumbling block

The issue of whether the likely cost-savings attributed to reduced antibiotic use (and reduced antibiotic-related adverse effects) would outweigh the accrued costs of PCT testing according to the described algorithms remains undefined. Current estimates in our institution (two different PCT suppliers), confirmed by independent authors in another continent [50], indicate a PCT cost per test of ~25–30 €, including expenses for all necessary measurements of calibrators, controls, and consumables, while the daily cost of antibiotic treatment for infections in ICU patients has been estimated between 114 and 384 € [50,51]. It is therefore of relevance to establish if PCT testing is cost-effective. Using a cost-minimization analysis, Heyland et al. found that, on average, PCT-guided therapy may save ~340 € per ICU patient. Similar savings (~320 €) were later estimated by Deliberato et al. [52]. However, these estimates were produced by applying data from controlled studies done in optimal conditions, with consistent application of PCT algorithms. As mentioned before, many clinicians may however be unwilling to interrupt antimicrobial therapies based on laboratory results and this can lead to a situation where a series of PCT measurements are done uselessly, therefore literally throwing “money down the drain” [53]. In our experience, daily PCT monitoring is often continued in many ICU patients for prolonged periods even though PCT concentrations in serum remain persistently low in relation to the peak value. To improve this situation, we recently decided to introduce a standard comment in the PCT report to alert intensivists when the 80% decrease from peak is reached. This has resulted in an overall 10% reduction of PCT requests. Managing the post-analytical phase of PCT testing in ICU may therefore help to improve the appropriateness of PCT request.

The UK National Institute for Health Research has issued a health technology assessment report evaluating the cost-effectiveness of PCT-guided antibiotic stewardship [54]. The document concluded that, according to the scientific evidence, PCT-guided algorithms might reduce

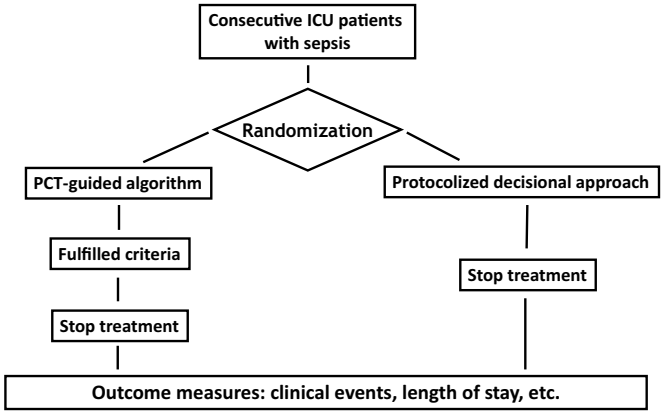


**Fig. 2.** Scheme for an outcome-based randomized trial evaluating procalcitonin (PCT)-guided algorithm. ICU, intensive care unit.

the antibiotic exposure in ICU patients with sepsis and in patients with RTIs presenting to the ED, without negative influences on clinical outcome but with a very small gain on quality-adjusted life years and economic savings. The authors concluded that further high-quality studies, in which the control arm is similar to the intervention arm in all respects other than the use of PCT testing, are needed to determine if any observed effects are due to the PCT itself or to the effect of introducing protocolized care. A scheme of how these outcome-based randomized trials should be designed is reported in Fig. 2 [55].

The Procalcitonin and Survival study was a randomized multicenter trial, recruiting 1200 patients in 9 ICU across Denmark, which evaluated whether daily PCT measurements and immediate diagnostic and therapeutic responses to abnormal values (defined as PCT $\geq 1.0$ μg/L) and day-to-day biomarker changes (< 10% decrease from the previous day) could reduce the 28-day mortality of critically ill patients [56]. The study found no difference in mortality between PCT and standard-of-care-only groups (hazard ratio: 0.98; 95% CI: 0.83–1.16). Furthermore, in the PCT arm, the length of stay in ICU was increased by one day ($P = 0.004$) and the duration of respiratory failure, determined by the rate of mechanical ventilation per ICU day, was increased by 4.9% (95% CI: 3.0%–6.7%). Finally, patients in the PCT group had a low estimated glomerular filtration rate for more days and needed dialysis for a longer time. The authors concluded that the PCT-guided strategy used in their trial did not improve survival and led to organ-related harm and prolonged ICU admission. Another recent randomized multicenter study, performed in a population of patients with suspected lower RTIs presenting to the ED, was also unable to show the superiority of PCT-guided approaches [57]. The provision of PCT values, along with instructions on their interpretation, did not result in a reduced use of antibiotics than did usual care.

## 7. Concluding remarks

In October 2015, the UK National Institute for Health and Care Excellence published a guidance on the use of PCT testing for diagnosing and monitoring sepsis [58]. After considering the available literature, the document concluded that there was not enough evidence to recommend the use of PCT to diagnose bacterial infection and guide decisions regarding antibiotic therapy. Nevertheless, PCT appears to be helpful in assisting intensivists in the decision to continue or stop antibiotics in acute RTIs patients [41]. If PCT-guided algorithms are consistently applied, they can help reduce hospitalization costs. Furthermore, PCT can be ordered in pediatrics, e.g. in neonates with suspected sepsis or children with suspected meningitis, even though confounding factors, such as physiological high biomarker levels in the first 72 h of life, should be known and considered.

Residual limitations include the high rate of non-compliance to PCT-driven protocols, the limited value of single PCT measurements and the elevated test costs (Table 3).

**Table 3**
Points to remember for an appropriate use of procalcitonin (PCT) testing.

- PCT is a poor diagnostic/prognostic marker for sepsis
- PCT is a reliable marker to assist intensivists in the decision to stop antibiotics. PCT-guided antibiotic duration is a validated approach to prevent antibiotic overconsumption in the intensive care unit setting
- PCT can be useful in pediatrics, but its interpretation can be complicated by some confounding issues
- Residual limitations include:
  - o High rate of non-compliance to PCT-driven protocols
  - o "Single" PCT measurement alone is of limited value
  - o High test cost
- There is not enough evidence to recommend wide PCT use in the health care system: vetting of PCT requests is recommended.

For all these reasons, it seems sensible that laboratories offer PCT testing to ICU (as an aid in decision for continuing or stopping antibiotics) and pediatric wards (as an aid for diagnosing late-onset sepsis in newborns or bacterial meningitis or pyelonephritis in children). For all other clinical wards, PCT requests should be guided by laboratory specialists, who should discuss with clinical requestors about the clinical suspicion supporting the PCT request in addition to other already available tests (e.g., CRP). This may help to improve request appropriateness and preserve the cost-benefit avoiding unnecessary testing [59].

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