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Comparison between B·R·A·H·M·S PCT direct, a new sensitive point-of-care testing device for rapid quantification of procalcitonin in emergency department patients and established reference methods – a prospective multinational trial

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Abstract

Background: Procalcitonin (PCT) is increasingly being used for the diagnostic and prognostic work up of patients with suspected infections in the emergency department (ED). Recently, B·R·A·H·M·S PCT direct, the first high sensitive point-of-care test (POCT), has been developed for fast PCT measurement on capillary or venous blood samples.
Methods: This is a prospective, international comparison study conducted in three European EDs. Consecutive patients with suspicion of bacterial infection were included. Duplicate determination of PCT was performed in capillary (fingertip) and venous whole blood (EDTA), and compared to the reference method. The diagnostic accuracy was evaluated by correlation and concordance analyses.
Results: Three hundred and three patients were included over a 6-month period (60.4% male, median age 65.2 years). The correlation between capillary or venous whole blood and the reference method was excellent: r^2=0.96 and 0.97, sensitivity 88.1% and 93.0%, specificity 96.5% and 96.8%, concordance 93% and 95%, respectively at a 0.25 µg/L threshold. No significant bias was observed (−0.04 and −0.02 for capillary and venous whole blood) although there were 6.8% and 5.1% outliers, respectively. B·R·A·H·M·S PCT direct had a shorter time to result as compared to the reference method (25 vs. 144 min, difference 119 min, 95% CI 110–134 min, p<0.0001).
Conclusions: This study found a high diagnostic accuracy and a faster time to result of B·R·A·H·M·S PCT direct in the ED setting, allowing shortening time to therapy and a more wide-spread use of PCT.

Keywords: antibiotic therapy; emergency department; infection; method comparison; point-of-care testing; procalcitonin.

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Introduction

Delays in diagnosis of bacterial infections and sepsis are the single most effective modifiable factor associated with poor sepsis outcome [1–4]. Rapid rule out and/or confirmation of sepsis is, therefore, an essential element in the initial work up of patients with suspicion of infection in the emergency department (ED). For this purpose, point-of-care testing (POCT) with a short time between sample acquisition and analysis of infection blood markers provides new opportunities. Effective use of POCT technology

in the ED has great potential to decrease delays in initiation of antimicrobial treatment and increase ED efficiency, by alleviating negative effects of overcrowding EDs [5]. POCT is performed directly at the patient bedside with minimal time delays due to absent preanalytics and transportation of samples to the central laboratory.

Procalcitonin (PCT), a biomarker of bacterial infections, is increasingly being used for early risk stratification of patients with suspected sepsis and for antibiotic stewardship [6, 7]. Due to higher specificity compared to more traditional markers, PCT helps in the differentiation of bacterial and viral infections [8]. In addition, a meta-analysis found an overall sensitivity of 77% and a specificity of 79% of PCT to distinguish between sepsis and systemic inflammatory response syndrome (SIRS) of non-infectious origin in critically ill patients [9]. In addition, several interventional trials found a marked reduction in overall antibiotic use and duration of antibiotic courses in patients with respiratory infections when PCT was used as a stewardship guide without compromising outcome [10–12]. Two of these trials were done in primary care practices where PCT was not measured on site but sent to a reference lab [13, 14]. A major limitation of current PCT testing is the lack of sensitive POCT which may help to have test results earlier and in smaller facilities without reference laboratories (i.e. smaller EDs, outpatient clinics).

A novel quantitative immunochromatographic whole blood POCT was developed. In accordance with CLSI (Clinical and Laboratory Standards Institute) guideline EP5-A the inter assay precision is <20% coefficient of variation (CV) at a 0.5 µg/L level; <15% at a ~2 µg/L level; <20% at a ~8 µg/L level and the functional assay sensitivity is <0.25 µg/L. Herein, we prospectively compared the performance between this new POCT and the reference method (B·R·A·H·M·S PCT sensitive Kryptor or Elecsys B·R·A·H·M·S PCT) in the ED routine terms in patients with suspicion of bacterial infection.

Materials and methods

Patients, setting, ethics

This is a prospective, comparative international multicenter study including ED patients with suspicion of bacterial infection undergoing routine care PCT measurement. Adult patients (age≥18 years) from three hospitals in Germany, France, and Switzerland were included between April 2013 and April 2014. Patients had to have a possible bacterial infection at initial presentation based on the assessment of the treating ED physicians, and be willing to give written informed consent. The exclusion criteria were non-adult patients (<18 years of age), pregnant or breastfeeding women, and persons incapable of acting in law. Data on demographics, diagnosis, laboratory parameters and site-of-care decision were assembled for each patient upon admission and during hospital stay.

The approval for this study was obtained from all Local Ethical Committees and all patients gave written informed consent. The study was registered in the "ClinicalTrials.gov" Database (http://www.clinicaltrials.gov/ct2/show/NCT01771029, identifier NCT01771029).

Objectives and evaluation plan

The primary objective of this study is to show an at least 90% correlation between B·R·A·H·M·S PCT direct™ and the PCT reference method within the measuring range of B·R·A·H·M·S PCT direct (0.1–10.0 µg/L) and a concordance for normal range and increased PCT concentrations at the clinical cut-off of 0.25 µg/L and 0.5 µg/L PCT. Previously, an excellent correlation and concordance was described comparing the two involved reference methods (B·R·A·H·M·S PCT sensitive™ Kryptor™ or Elecsys® B·R·A·H·M·S PCT™) [15], meaning there was no measuring discrepancy between the reference methods. The secondary objective of this study is to compare time to result of the B·R·A·H·M·S PCT direct with the reference methods.

To perform the method comparison, one ethylenediaminetetraacetic acid (EDTA) blood sample and two fingertip blood samples were collected from each included patient at the same time point. For duplicate determination of all blood samples two distinct readers were used.

Blood taking

Because of the limited stability of the used specimen type (whole blood) a retrospective freezer evaluation with native patient samples was not possible. The prospective evaluation was designed with a minimum additional intervention for each patient. For the evaluation, 20 µL capillary blood of fingertip and one tube (approximately 5 mL) EDTA whole blood (taken from the routine blood withdrawal) from each enrolled patient was needed. The EDTA whole blood/plasma was used for the method comparison and for the technical evaluation. Results of B·R·A·H·M·S PCT direct did not influence any clinical decision and were noted in a blinded form. The blood samples were used for immediate measurement of the B·R·A·H·M·S PCT direct assay (20 min measuring time). Subsequently, the remaining sample volume of EDTA blood was centrifuged and the resulting plasma analysed by a PCT reference method. As a reference method, in France and Switzerland the Kryptor (ThermoFisher) device was used, whereas in Germany the Elecsys (Roche) system was available. The remaining plasma was deep-frozen at –20 °C for later analysis of all samples evaluating concordance to further PCT reference methods.

Sample size calculation

Overall test accuracy was calculated as the proportion of subject samples categorised correctly by B·R·A·H·M·S PCT direct test vs. the reference method (sum of true positives and true negatives divided by the total number of samples). Assuming that the concordance between the two assays is at least 93%, a total of 171 unique subject

samples will provide an estimate that is within ±3% of the true value with 90% confidence. If the concordance is at least 95%, 80 samples are sufficient to provide an estimate ±5% of the true value with 95% confidence. Due to the supposed high variability in clinical real-life conditions we aimed to collect at least 200 unique subject samples in order to be able to demonstrate that the concordance is larger than 90%.

Statistics

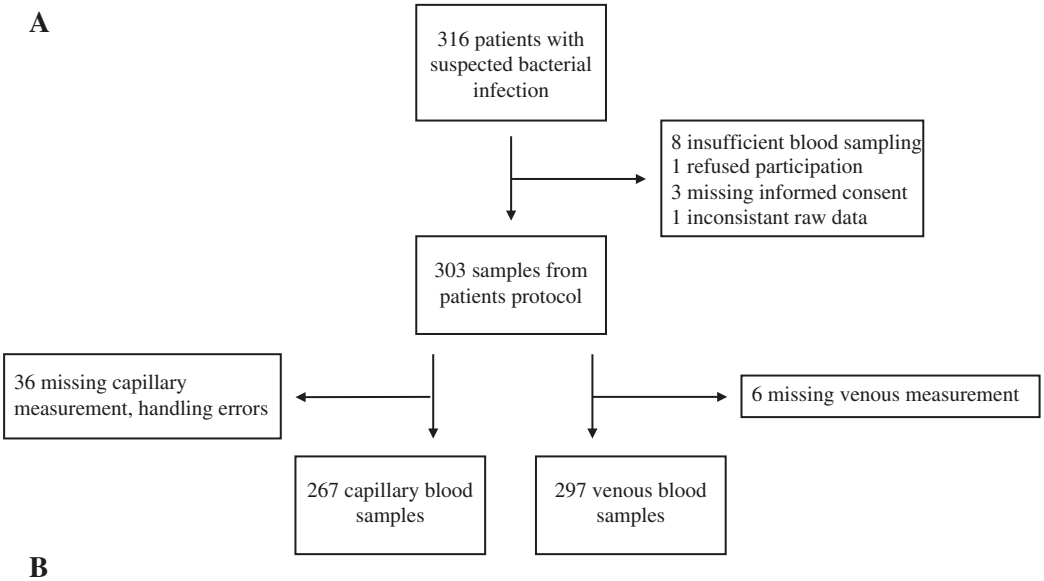
Discrete variables are expressed as counts (percentage) and continuous variables are expressed as medians and interquartile ranges (IQR: 25th–75th percentiles) unless stated otherwise. Duplicate B·R·A·H·M·S PCT direct values were averaged and the mean was taken for further analysis. All testing was two-tailed and $p<0.05$ were considered to indicate statistical significance. Comparison of B·R·A·H·M·S PCT direct and the reference method was evaluated by the Passing and Bablok regression analysis and a Bland-Altman difference plot. In the latter, the mean PCT levels of both methods are plotted on the x-axis and the mean difference, as an absolute deviation, on the y-axis. Clinical concordance between B·R·A·H·M·S PCT direct and the reference method over two clinically relevant PCT cut-offs (0.25 µg/L and 0.5 µg/L) was assessed by calculating the κ coefficient. Analyses were performed with STATA 12.1 (Stata Corp., College Station, TX, USA) and Analyse-it for Microsoft Excel.

Results

Patient population and baseline characteristics

A total of 303 ED patients (60.4% male, median age 65.2 years) were included for this comparison study. From these, 36 capillary and six venous measurements were missing due to handling errors (Figure 1A). From the remaining 267 B·R·A·H·M·S PCT direct capillary samples, 151 (56.6%) samples had a PCT value of 0.25 µg/L or below. In B·R·A·H·M·S PCT direct venous samples 159 of 297 patients (53.5%) showed a PCT value of 0.25 µg/L (clinically relevant for decision to initiate/discontinue antibiotic therapy) or

A



B

	Patients, n	PCT <0.1 µg/L	PCT 0.1- ≤ 0.25 µg/L	PCT >0.25- ≤ 0.5 µg/L	PCT >0.5- <10.0 µg/L	PCT ≥ 10.0 µg/L
B·R·A·H·M·S PCT direct capillary	267	56	95	31	76	9
B·R·A·H·M·S PCT direct venous	297	66	93	33	93	12
Reference	303	81	79	42	83	18

Figure 1: (A) Flow diagram of patient enrolment; (B) PCT level distribution according to the measuring range. PCT, procalcitonin.

below. 202 (75.7%) B·R·A·H·M·S PCT direct capillary and 219 (73.7%) B·R·A·H·M·S PCT direct venous measurements were within the measuring range (Figure 1B).

Baseline characteristics of the overall cohort and separated by clinical centre are depicted in Table 1. Overall, 183 blood cultures were taken, whereof 30 (16.4%) were positive. A total of 162 (53.5%) patients had a final ED diagnosis of a bacterial infection and 243 (80.2%) patients were finally admitted to the hospital at which 23 (7.6%) patients had to be transferred to the intensive care unit (ICU) over the course of hospital stay.

Comparison B·R·A·H·M·S PCT direct vs. reference method

Comparison of B·R·A·H·M·S PCT direct (values within the measuring range [0.1–10.0 μg/L]) with the reference method was performed in all cases with PCT measurements available from both methods. Regression analysis of B·R·A·H·M·S PCT direct capillary (n=202) and venous (n=219) samples and the reference method showed a very high correlation (r^2=0.97, slope: 0.90 [95% CI: 0.86–0.96], intercept: 0.03 [95% CI: 0.02–0.04] and r^2=0.95, slope: 0.98 [95% CI: 0.93–1.02], intercept: 0.02 [95% CI: 0.01–0.03], respectively; Figure 2A and B). Accordingly, the correlation between capillary and venous samples on B·R·A·H·M·S PCT direct (n=194) – excluding samples with PCT outside the detection range – showed the following parameters: r^2=0.98, slope: 1.01 [95% CI: 1.00–1.05], intercept: −0.00 [95% CI: 0.01–0.00] (Figure 2C). Based on this regression analysis, the clinically most relevant decision points (e.g. 0.25 μg/L and 0.5 μg/L) on the B·R·A·H·M·S PCT direct were not altered (data not shown).

The concordance between B·R·A·H·M·S PCT direct and the reference method at a clinically relevant PCT cut-off (0.25 μg/L) was 92.5% for capillary and 94.9% for venous samples. A PCT cut-off at 0.5 μg/L also revealed high percentages of agreement for capillary (96.3%) and venous samples (96.6%). As illustrated in Table 2, B·R·A·H·M·S PCT direct showed a very high sensitivity at a 0.25 μg/L cut-off in both capillary (88.9% [95% CI: 0.82–0.94]) and venous samples (93.7% [95% CI: 0.88–0.97]).

Even more sensitive were the results considering the 0.5 μg/L cut-off, 94.2% (95% CI: 0.87–0.98) in capillary and 98.0% (95% CI: 0.93–1.00) in venous measurements. The specificity ranged between 95.9% and 97.2% in all categories. Concordance levels ranged between 93% in capillary samples at the 0.25 μg/L cut-off and 97% in venous samples at the 0.5 μg/L cut-off.

For capillary and venous B·R·A·H·M·S PCT direct measurements the mean difference (95% limits of agreement) to the reference method was −0.05 (–1.226 to 1.126) and 0.023 (–1.014 to 1.060), respectively (Figure 3). Any bias could not be detected, however we identified some outlying PCT values, mainly in the high-value category.

Time to result B·R·A·H·M·S PCT direct vs. reference method

As shown in Figure 4, the overall time to result could be significantly reduced by using the B·R·A·H·M·S PCT direct assay. Overall, we found a mean time reduction of 119 min between the POCT and the reference methods namely from 2 h 24 min to 25 min (p=0.0001).

Discussion

This is the first study comparing the new B·R·A·H·M·S PCT direct assay with a laboratory based automated reference

Table 1: Baseline characteristics.

Parameter	All (n=303)	Germany (n=53)	France (n=118)	Switzerland (n=132)	p-Value
Demographics					
Age, years; median (IQR)	67.9 (54.6–79.3)	69.8 (60.1–78.0)	64.6 (46.8–84.2)	69.0 (57.7–78.2)	0.5070
Men, n (%)	184 (60.7)	30 (56.6)	72 (61.0)	82 (62.1)	0.7835
Diagnostics, n (%)					
Blood culture collected	183 (60.4)	30 (56.6)	50 (42.4)	103 (78.0)	0.0001
Positive blood cultures	30 (16.4)	5 (16.7)	3 (6.0)	22 (21.4)	0.6321
Primary diagnosis					
Bacterial infection	162 (53.5)	39 (73.6)	39 (33.1)	84 (63.6)	0.0001
Hospital admission, n (%)	243 (80.2)	46 (86.8)	71 (60.2)	126 (95.5)	0.0001
ICU admission, n (%)	23 (7.6)	7 (13.2)	12 (10.2)	4 (3.0)	0.5408
PCT auto μg/L; median (IQR)	0.21 (0.09–0.87)	0.13 (0.08–0.70)	0.13 (0.07–0.36)	0.44 (0.14–1.72)	0.0001

PCT, procalcitonin; ICU, intensive care unit; IQR, interquartile range; auto, automated (reference method).

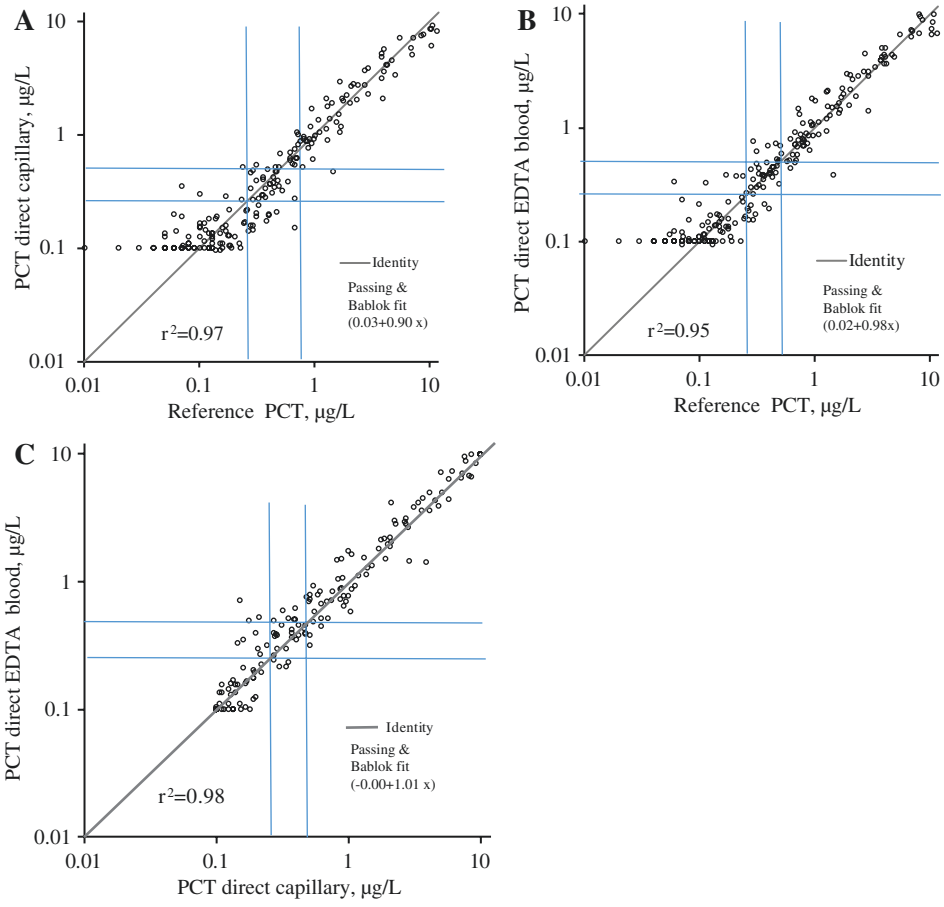


Figure 2: Correlation of averaged duplicate B·R·A·H·M·S PCT direct values and reference method.
(A) Capillary vs. reference method; (B) venous vs. reference method; (C) capillary vs. venous; PCT, procalcitonin; blue lines indicating 0.25 and 0.5 µg/L cut-offs, respectively.

Table 2: Diagnostic accuracy of B·R·A·H·M·S PCT direct at clinically relevant PCT cut-offs.

Cut-off, µg/L	0.25 µg/L			0.5 µg/L		
	Sens., % (95% CI)	Spec., % (95% CI)	Concordance, %	Sens., % (95% CI)	Spec., % (95% CI)	Concordance, %
B·R·A·H·M·S PCT direct capillary						
n=267	88.9 (0.82–0.94)	96.5 (0.92–0.99)	92.5	94.2 (0.87–0.98)	97.2 (0.94–0.99)	96.3
B·R·A·H·M·S PCT direct venous						
n=297	93.7 (0.88–0.97)	96.8 (0.93–0.99)	94.9	98.0 (0.93–1.00)	95.9 (0.92–0.98)	96.6

PCT, procalcitonin; Sens., sensitivity; Spec., specificity; CI, confidence interval.

method (Kryptor or Elecsys) for measurement of PCT in the ED setting. As a primary result, a high correlation was found without a clinically significant bias. In addition, time to result was markedly reduced compared to the reference method measurement.

In the last decade, other quantitative automated options for PCT testing have been described, including the Liaison BRAHMS PCT (DiaSorin) [16], Elecsys BRAHMS PCT (Roche Diagnostics) [15], Advia Centaur BRAHMS PCT (Siemens) [17] and VIDAS (bioMérieux) [18] with good correlation but missing important characteristics of a POCT application.

Recently, a new, highly sensitive fluorescence immune assay for a TIRF (total internal reflection)-based POCT

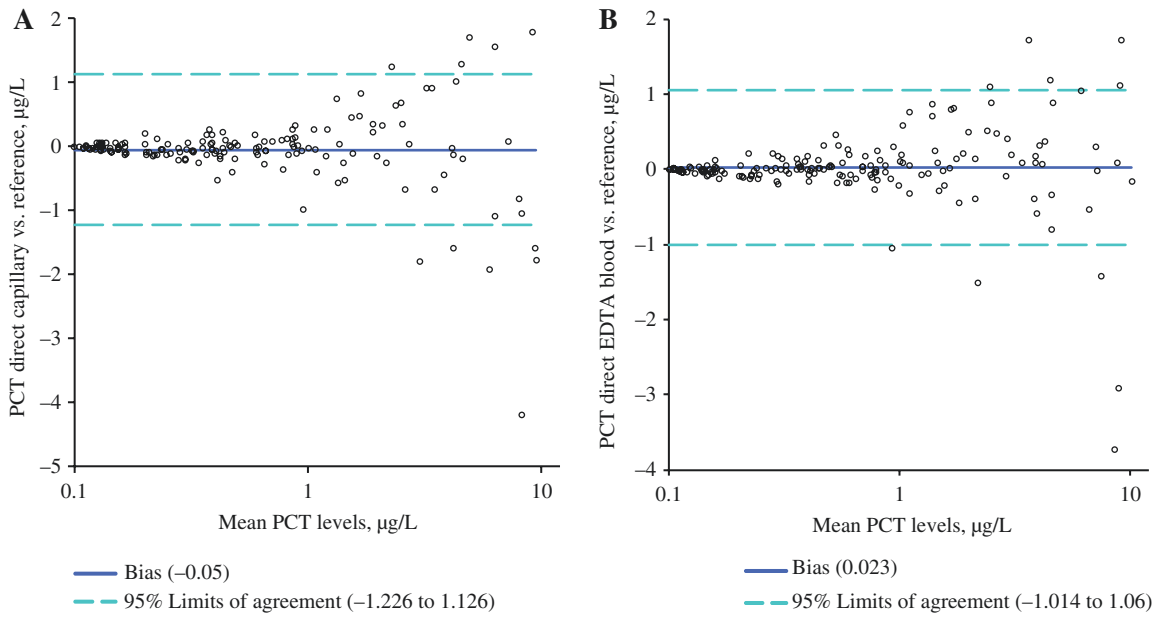


Figure 3: Comparison of averaged duplicate B·R·A·H·M·S PCT direct values and reference method.
(A) Capillary vs. reference method; (B) venous vs. reference method; PCT, procalcitonin.

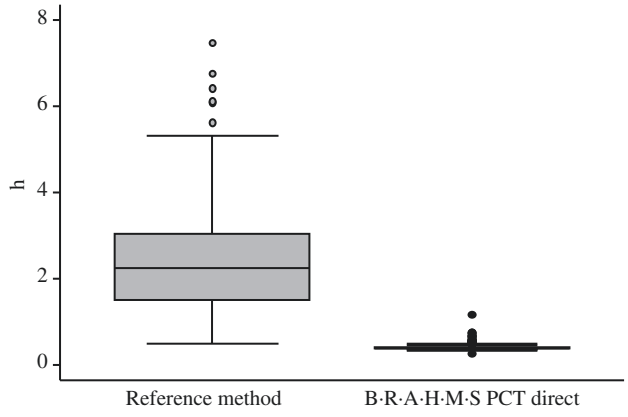


Figure 4: Time to result: B·R·A·H·M·S PCT direct vs. reference method.
p<0.0001.

device was developed for the detection of PCT [19]. They tested for the first time a diagnostic device for sepsis to use whole blood, which is a crucial requirement for POCT and were able to detect native PCT in patient samples with a good correlation compared to the Kryptor. Similar to the above mentioned POCT, the B·R·A·H·M·S PCT direct fulfills all the essential characteristics of a POCT including a small – and easy to handle-sample volume (20 µL), a high sensitivity, a clinically relevant measuring range (0.1–10.0 µg/L) and a fast time to result.

In contrast to the others studies, we also performed real-life time to result ascertainments from the bedside blood collection to the print-out of the measurement. A further strength is the prospective multicenter character of this study conducted under clinical routine conditions in different countries and health care systems. These characteristics are important for underlining the suitability for daily use in the EDs with low variability.

In clinical routine, PCT cut-off ranges are often used to guide initiation and duration of antimicrobial treatment [20, 21]. In this context, our findings showing a high correlation of the new POCT with the reference methods across cut-off ranges are reassuring. First, the Bland-Altman plot did not show any relevant bias comparing capillary and venous B·R·A·H·M·S PCT direct measurements as well as B·R·A·H·M·S PCT direct and reference method measurements. Because we did not re-perform a concordance analysis between the two involved reference methods and accepted – based on a previous publication [15] – the pre-calculated concordance, a certain impreciseness cannot be completely excluded. Secondly, the data from three tertiary care hospitals in Europe show a high concordance (≥93%) over both relevant critical decision PCT cut-offs (0.25 µg/L and 0.5 µg/L) without a significant change in frequency distribution. Given the limitation that we did not perform a state-of-the-art precision calculation, we assume – based on these findings – B·R·A·H·M·S PCT direct PCT measurements would lead to the same decision for or against initiating antibiotic therapy as compared to the reference method. Furthermore, B·R·A·H·M·S PCT direct could serve as a solid basis to develop more POCT

systems in the future involving other biomarkers. In this case, an indispensable condition is to directly link the POCT system to the clinic software, to avoid manual data input. If implemented, POCT may increase ED effectiveness and thereby helps to lessen the burden of overcrowding, decrease time to antibiotic therapy and improve risk stratification without delaying patient management decisions. Until now, available POCT systems involving other sepsis biomarker (e.g. lactate) were associated with reduced turnaround times, without investigating medical outcome [22], however a separate study found improved outcomes in patients with higher lactate clearance compared with patients with lower clearance [23]. This relationship between time-to-treatment initiation and patient outcome highlights the need for expedited diagnosis through POCT. This study is obviously unable to proof this hypothesis, however, future evaluations should address this important aspect of POCT as already stated by a recent review asking about evidence of using POCT [24].

PCT protocols have been used mainly for management of in-hospital and intensive care patients mainly because of the more wide-spread availability of assays in these settings. Arguably, the most important antibiotic overuse occurs in the outpatient/general practitioner (GP) setting. Previous randomized trials have found important reductions in antibiotic use in outpatients associated with the use of PCT testing [13, 14]. As a major limitation, in these studies samples were sent to a core laboratory due to the lack of smaller PCT testing devices. The new high sensitive POCT technology may also open the door for a more wide spread use of PCT in the setting of outpatients and GPs.

Conclusions

B·R·A·H·M·S PCT direct, a new, sensitive POCT assay for PCT quantification was developed. The device conforms to all the important characteristics of a POCT application, such as a small sample volume, a high sensitivity, and a fast time to result under the routine terms. Samples must not be pretreated because the device uses ready-to-use cartridges. Furthermore, it is safe and simple to handle. To our best knowledge, this is the first time that a measurement system for quantifying PCT under the terms of daily clinical emergency practice was developed that can be applied in whole blood samples.

The PCT assay on the B·R·A·H·M·S PCT direct shows an excellent correlation and concordance with the established reference method. Additionally, the data support the use of the same nominal PCT cut-offs previously established for this application. This is highly relevant for the routine implementation of PCT as a biomarker for antibiotic decision making in the ED setting. Due to a missing state-of-the-art precision analysis results must be interpreted in the clinical context of the patient.

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