Ferruccio Ceriotti[a,*], Irene Marino, Andrea Motta and Anna Carobene

Analytical evaluation of the performances of Diazyme and BRAHMS procalcitonin applied to Roche Cobas in comparison with BRAHMS PCT-sensitive Kryptor

https://doi.org/10.1515/cclm-2017-0159
Received February 24, 2017; accepted July 12, 2017; previously published online August 15, 2017

Abstract

Background: Procalcitonin (PCT) is a recognized marker of sepsis, and its use is expanding to antibiotic stewardship. The aim of this study was the evaluation of two methods: Diazyme PCT on Roche Cobas c702 (PCT-D) and BRAHMS PCT on Roche Cobas e602 analyzers (PCT-BR) in comparison with BRAHMS PCT-sensitive Kryptor (PCT-BK).

Methods: Imprecision was assessed at six critical concentrations following the CLSI EP5-A3; limits of detection (LoDs) were checked according to CLSI EP17-A2; linearity was tested, and method comparison was performed on 239 serum samples.

Results: Overall CVs ranged from 12.58% to 5.97% for PCT-D, from 3.94% to 1.70% for PCT-BR and from 6.57% to 1.90% for PCT-BK. LoDs were 0.143 μg/L, 0.014 μg/L, 0.040 μg/L for PCT-D, PCT-BR and PCT-BK, respectively. The functional assay sensitivity was 0.24 μg/L for PCT-D, 0.045 μg/L for PCT-BK and <0.035 μg/L for PCT-BR. PCT-BR was linear up to 68.7 μg/L, PCT-BK up to 43 μg/L and PCT-D up to 27.2 μg/L. Method comparison: PCT-D = 0.6543 PCT-BK + 0.014, r = 0.8463 (but 0.44 if calculated on 0–5 μg/L range); PCT-BR = 0.9125 PCT-BK + 0.021, r = 0.9917. Cohen's κ ranged from 45.2% at 0.25 μg/L to 57.0% at 2.00 μg/L between PCT-D and PCT-BK, whereas it ranged from 89% to 81.3% between PCT-BR and PCT-BK.

Conclusions: The PCT-D performances were significantly different from those of PCT-BR and PCT-BK regarding sensitivity, precision, linearity and agreement at clinical cutoffs. For some patients with serial testing, significantly deviating results were obtained compared to reference. In contrast to Roche PCT assay, it does not seem feasible to use BRAHMS PCT cutoffs for the Diazyme test.

Keywords: measurement; performance evaluation; procalcitonin; sepsis marker.

Introduction

Procalcitonin (PCT) is a soluble protein released into circulation in response to significant systemic inflammation, mainly caused by bacterial origin [1]. It is a recognized marker of bacterial infection, in well-defined clinical subsets, and sepsis [2]. Elevated PCT concentrations have a high positive predictive value for the diagnosis of sepsis, severe sepsis or septic shock (PCT >0.5 to >2 μg/L). On the contrary, normal or very low PCT plasma concentrations have a high negative predictive value to rule out severe systemic inflammation or sepsis (PCT <0.25 to <0.5 μg/L) [1] and provide guidance to the physician to re-assess the suspected diagnosis.

Reference individuals without any bacterial infection usually have PCT levels <0.05 μg/L (97.5th percentile) when measured with an ultrasensitive test [3], and found clearly below 0.1 μg/L when measured with any of the currently available sensitive PCT tests used in clinical routine. Various clinical cutoffs for PCT are established for various clinical settings, with higher cutoffs being used in critical care and sepsis and lower cutoffs being used in immunocompromised patients, or to guide antibiotic decisions [4]. PCT-based clinical algorithms have been proposed to guide antibiotic therapy both for patients with lower respiratory tract infections (LRTI), including pneumonia, acute exacerbations of chronic obstructive pulmonary disease and acute bronchitis as well as for critically ill patients [5–8]. The use of PCT in community acquired pneumonia has also been proposed both for adults [9] and children [10]. Both the use as a marker of bacterial infection, in well-defined clinical subsets and sepsis and as antibiotic guidance, rely on the above-mentioned decision limits.

[a]Present address: Central Laboratory, IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 28, 20122 Milano, Italy.
***Corresponding author: Ferruccio Ceriotti,** Clinical Laboratory Service, San Raffaele Hospital, Via Olgettina 60, 20132 Milan, Italy, Phone: +39 0226432282, Fax: +390226432640, E-mail: ceriotti.ferruccio@hsr.it
Irene Marino, Andrea Motta and Anna Carobene: Clinical Laboratory Service, San Raffaele Hospital, Milan, Italy

Moreover, the use of PCT in different contexts increases the importance of the measurements in the low range. Further, it is important that PCT levels are not only interpreted strictly in the context of the clinical setting, but also considering the technical performance of the particular PCT assay used [4]. The latter is of relevance as the clinical cutoffs have been set up using the BRAHMS PCT-sensitive Kryptor assay, so to use the same limits with different methods requires a very good analytical performance and comparability with the predicate method.

The scope of the work was to analyze the assay performance of Diazyme PCT (application on COBAS system c702) (PCT-D) and Elecsys BRAHMS PCT (on COBAS e602) (PCT-BR) in comparison with BRAHMS PCT-sensitive Kryptor (PCT-BK).

Materials and methods

The Diazyme PCT (Diazyme Laboratories, Poway, CA, USA) was installed on the module c702 of a Roche Cobas 8000 (Roche Diagnostics) following the instructions of the manufacturer. The Elecsys BRAHMS PCT (Roche Diagnostics) was installed on the module e602 of the same Roche analyzer, BRAHMS PCT-sensitive Kryptor (Thermo Fisher Scientific, BRAHMS GmbH) was measured on the Kryptor Compact Plus instrument.

Evaluation of imprecision

The experiment was performed according to the CLSI document EP05-A3: duplicate measurements in two runs per day over 20 days (80 measurements per sample) with the three methods under evaluation [11]. Four serum pools were prepared from routine leftover samples at concentrations close to the decision limits and two control materials (CTR_PCTL1 and 2, lot 105150 [Diazyme] for PCT-D; CTR_PCT1 lot 131981 and CTR_ PCT2 lot 131983 [Thermo Fisher] for PCT-BR; CTR_PCT 1 and 2 lot 25030 [Thermo Fisher] for PCT-BK).

Limit of detection (LoD) was defined according to the CLSI document EP17-A2 [12]. Ten pools with PCT concentrations close to the LoD declared by the manufacturers were prepared from routine leftover samples. The same pools were used for PCT-BR and PCT-BK, whereas a different set of pools was used for PCT-D. Each pool was measured in duplicate in five different days. The CV obtained on the 10 pools were used to define a precision profile to calculate the functional sensitivity. A specific limit of blank (LoB) study was not performed, and the LoB magnitude was extrapolated from the SD obtained in the LoD study.

Linearity

A high concentration sample was diluted in a scalar mode with a low concentration pool. The 11 dilutions were measured in triplicate with the three methods. The plotted data were visually inspected, and a least square linear regression was performed using only the points in the linear part of the plot. Deviation from linearity was assessed according to CLSI EP6-A [13].

Method comparison

Two hundred and thirty-nine serum samples were selected from clinical laboratory routine in order to cover adequately the whole concentration range, with a sample distribution that reflects the average distribution of PCT measurements in clinical routine in our laboratory. Each sample was measured with the three methods on the same day, or at maximum 24 h apart. Between measurements, samples were stored capped at 2–8 °C. PCT-D and PCT-BR were measured on the same aliquot on the two modules (c702 and e602) of the same Roche Cobas 8000 analytical system. The measurements were performed during a period of 3 months (September–November 2016) using two different lots of reagents for each of the three methods.

Statistical analyses

Statistical analyses regarding the method comparisons were done with R version 3.1.2 [14], deploying packages “mcr” 1.2.1. [15], using the Passing-Bablok approach [16].

Ethical approval

The evaluation was performed on pre-existing inpatient serum samples referred for routine PCT testing, and the material was obtained after routine analysis was completed. Therefore, no institutional review board approval was necessary. The research complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research.

Results

Imprecision

The results of the three methods are shown in Table 1. The analysis of variance allows to separate the different sources of variability. The overall CV ranged from 12.58% to 5.97% for PCT-D, from 3.94% to 1.70% for PCT-BR and from 6.57% to 1.90% for PCT-BK.

Limits of detection

The calculated LoDs were 0.143 µg/L, 0.014 µg/L and 0.040 µg/L for PCT-D, PCT-BR and PCT-BK, respectively. The functional sensitivity (concentration where CV = 20%) was 0.24 µg/L for PCT-D and 0.045 µg/L for PCT-BK,

Table 1: Results of the evaluation of imprecision.

		Pool 1	Pool 2	Pool 3	Pool 4	Ctrl low	Ctrl high
Diazyme PCT on COBAS c702	**Mean, µg/L**	**0.50**	**0.67**	**1.57**	**6.05**	**1.46**	**13.70**
	$CV_{repeatability}$	10.70%	6.98%	5.16%	2.13%	3.51%	3.35%
	$CV_{between\ run}$	1.30%	3.66%	3.20%	5.57%	3.19%	3.88%
	$CV_{between\ day}$	6.49%	6.68%	1.52%	0.00%	4.22%	3.50%
	$CV_{within\ lab}$	**12.58%**	**10.33%**	**6.26%**	**5.97%**	**6.35%**	**6.21%**
	Mean, µg/L	**0.64**	**1.13**	**2.38**	**7.64**	**0.49**	**10.09**
BRAHMS PCT on COBAS e602	$CV_{repeatability}$	1.97%	1.35%	1.71%	1.36%	2.38%	1.17%
	$CV_{between\ run}$	3.41%	2.92%	1.76%	1.55%	0.80%	1.19%
	$CV_{between\ day}$	0.00%	0.00%	0.00%	0.00%	1.57%	0.30%
	$CV_{within\ lab}$	**3.94%**	**3.22%**	**2.45%**	**2.07%**	**2.96%**	**1.70%**
	Mean, µg/L	**0.69**	**1.22**	**2.67**	**8.34**	**0.26**	**10.23**
BRAHMS PCT on Kryptor	$CV_{repeatability}$	2.27%	1.69%	1.15%	0.78%	4.87%	0.79%
	$CV_{between\ run}$	2.44%	3.28%	1.66%	1.73%	0.00%	2.06%
	$CV_{between\ day}$	0.00%	0.00%	0.46%	0.00%	4.42%	1.59%
	$CV_{within\ lab}$	**3.33%**	**3.69%**	**2.07%**	**1.90%**	**6.57%**	**2.72%**

$CV_{repeatability}$, variability of duplicates; $CV_{between\ run}$, variability between morning and afternoon run. The four pools were the same for the three methods, whereas control materials were method specific. Bold identifies mean values and $CV_{within\ lab}$.

whereas for PCT-BR, the CV obtained at 0.05 µg/L was only 7.6% (Figure 1).

Linearity

All the three methods showed deviation from linearity at the low range (difference between the second-order [quadratic] model and the first-order [linear] >20% at the lowest concentration tested). Only the PCT-BR was linear up to the highest concentration tested (68.7 µg/L) (r = 0.9987) (differences between second and first-order model always <5%). The PCT-BK provided linear results up to 43 µg/L (r = 0.9988). The last concentration where PCT-D showed a linear response was 19.5 µg/L (r = 0.9955). In a second experiment with a lower concentration sample, PCT-D showed linearity up to 27.2 µg/L (r = 0.9977) (see Supplemental Figure 1 for details).

Method comparison

The patient samples were selected from routine within the linearity limit of the PCT-D method with a sample distribution that reflects the average distribution of PCT measurements in clinical routine. The results are presented in Figures 2 and 3. The regression equations according to Passing-Bablok are the following: PCT-D = 0.6543 PCT-BK + 0.014; PCT-BR = 0.9125 PCT-BK + 0.021. The Pearson correlation coefficients (r) were 0.85 and 0.99, respectively, whereas in the clinically most relevant range, that is for PCT-BK values smaller than 5 µg/L, the correlation coefficients were PCT-D vs. PCT-BK = 0.44; PCT-BR vs. PCT-BK = 0.99.

The level of concordance of the three methods at the different clinical cutoffs is described in Table 2. At the clinical relevant cutoff of 0.25 µg/L, the concordance between the Kryptor and the Diazyme PCT assay was only 78.2% (Cohen's κ 45.2%), and at the cutoff 0.5 µg/L, the

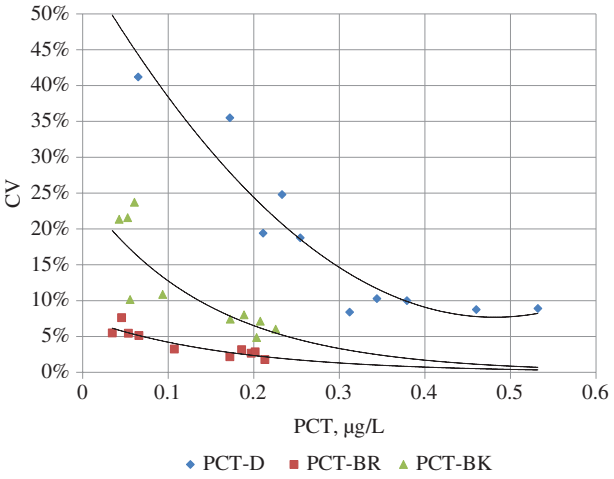

Figure 1: Imprecision profile for the definition of the functional assay sensitivity of the three methods.
Each dot represents the CV% of 10 measurements (duplicate measures in five different days). The same pools were used for PCT-BR and PCT-BK, whereas a different set of pools was used for PCT-D.

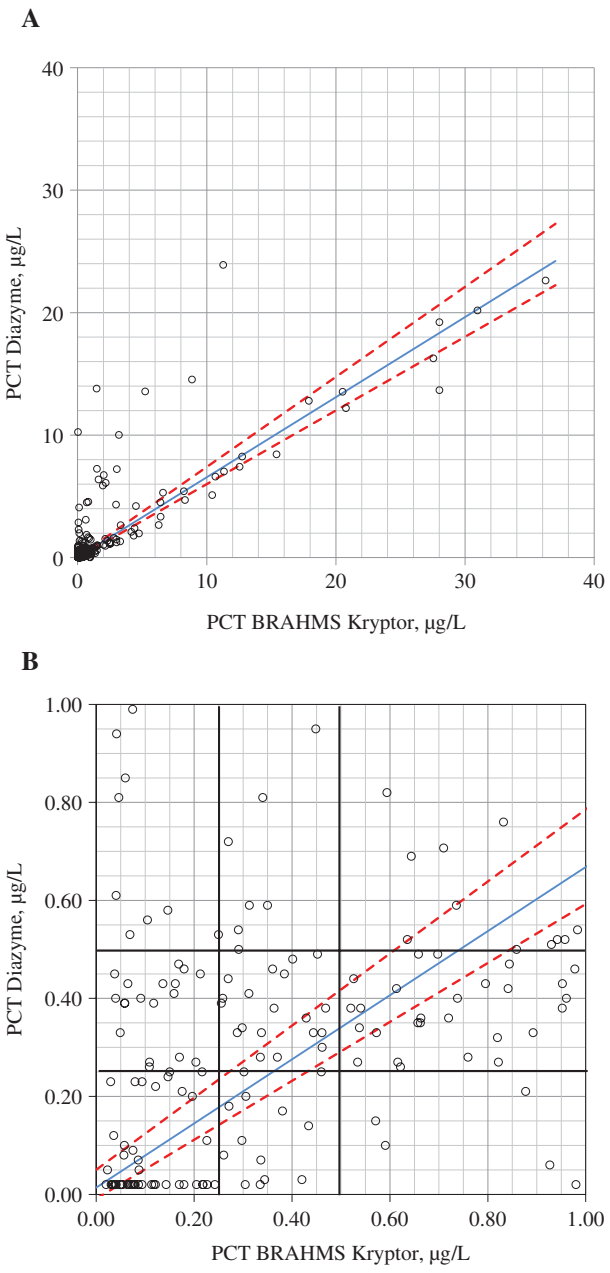

Figure 2: (A) Correlation between PCT-D and PCT-BK, dotted lines represent the 0.95 – confidence bounds calculated with the bootstrap (quantile) method. (B) It represents the expansion of the range 0–1.0 µg/L of figure 2A. The thick lines identify the clinical cutoffs of 0.25 and 0.50 µg/L, the blue and red dotted lines as in (A).

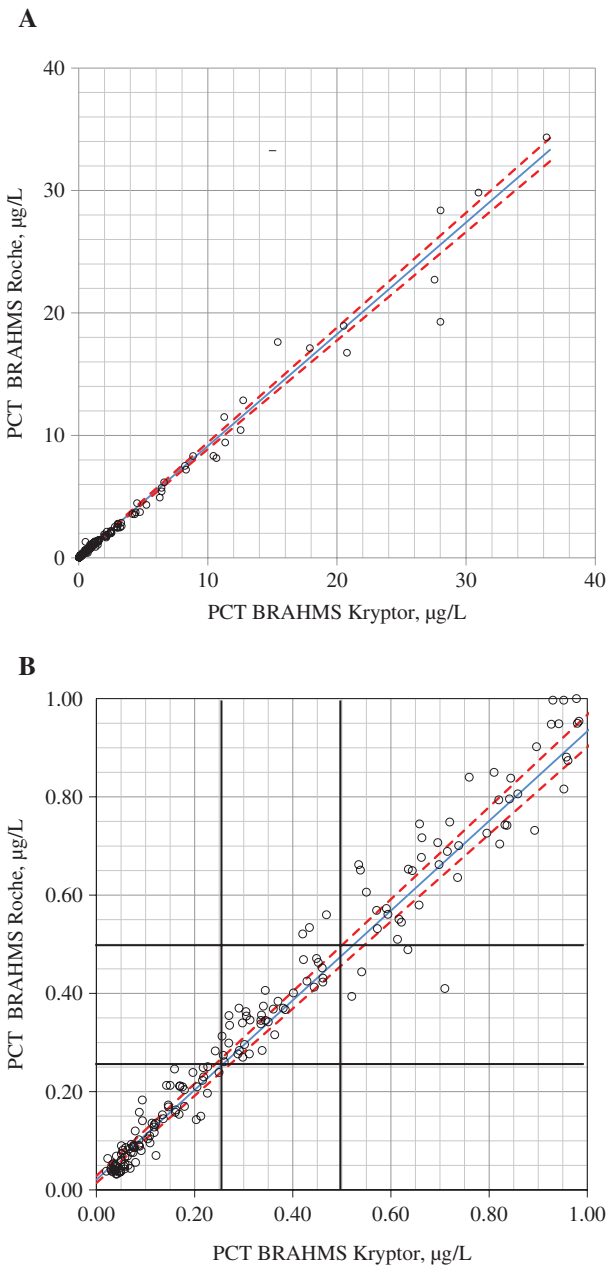

Figure 3: (A) Correlation between PCT-BR and PCT-BK, dotted lines represent the 0.95 – confidence bounds calculated with the bootstrap (quantile) method. (B) It represents the expansion of the range 0–1.0 µg/L of figure 3A. The thick lines identify the clinical cutoffs of 0.25, 0.50 µg/L, the blue and red dotted lines as in (A).

concordance between the two methods was only 74.5% (Cohen's κ 44.9%) (Table 2).

For some patients, serial PCT values were available. PCT-BK and PCT-BR in all cases demonstrated high correlation over the entire time course while PCT-D for some samples presented a response completely different from PCT-BK/PCT-BR with values up to 10 times higher or more. This difference was reproducible and consistent over different samples from the same patient, and generally (but not always) in line with the septic state of the patient, an example is presented in Figure 4, patient A. Moreover, we documented five cases with very high PCT-D (in four cases >25 µg/L), with completely normal PCT-BK and/or PCT-BR (<0.1 µg/L) and absence of clinical signs of sepsis. Other

Table 2: PCT measurements, comparison of Diazyme and BRAHMS reagents on Roche COBAS 8000 vs. BRAHMS Kryptor.

	Clinical cutoff, µg/L	Negative agreement (95% CI)	Positive agreement (95% CI)	Total agreement	Cohen's κ (95% CI)	Number (n) of	
						False negatives	False positives
Diazyme vs. BRAHMS Kryptor	**0.25**	**57.1%** (45.9%–67.9%)	**89.7%** (83.9%–94.0%)	**78.2%**	**45.2%** (33.4%–57.0%)	**16**	**36**
	0.50	**80.6%** (72.6%–87.2%)	**67.8%** (58.5%–76.2%)	**74.5%**	**44.9%** (34.1%–55.7%)	**37**	**24**
	1.00	**91.4%** (86.2%–95.1%)	**78.5%** (66.5%–87.7%)	**87.9%**	**62.8%** (52.0%–73.5%)	**14**	**15**
	2.00	**94.3%** (90.0%–97.1%)	**69.6%** (54.2%–82.3%)	**89.5%**	**57.0%** (43.8%–70.2%)	**14**	**11**
BRAHMS Roche vs. BRAHMS Kryptor	**0.25**	**96.4%** (89.9%–99.3%)	**100.0%** (97.6%–100.0%)	**98.7%**	**89.0%** (83.1%–94.8%)	**0**	**3**
	0.50	**97.6%** (93.1%–99.5%)	**96.5%** (91.3%–99.0%)	**97.1%**	**86.9%** (80.8%–92.9%)	**4**	**3**
	1.00	**98.3%** (95.0%–99.6%)	**96.9%** (89.3%–99.6%)	**97.9%**	**85.6%** (78.5%–92.6%)	**2**	**3**
	2.00	**100%** (98.1%–100.0%)	**89.1%** (76.4%–96.4%)	**97.9%**	**81.3%** (72.1%–90.5%)	**5**	**0**

Level of concordance evaluated at different clinical cutoffs. The clinical cutoff 0.1 µg/L was not considered for analysis because of the low sensitivity of the PCT-D which would not allow differentiation at this cutoff (PCT-D: LoD = 0.14 and FAS = 0.24 µg/L).

examples of patients with discrepant results are presented in Figure 4 (patients B and C), whereas patient D represents a case of similar profile of PCT course but still different PCT concentration between PCT-D vs. PCT-BK/PCT-BR.

Discussion

Performance assessment

For the three methods, the observed level of imprecision is in line with the specifications of the manufacturers [17–19]. The imprecision is significantly lower for the BRAHMS PCT on both analyzers (Roche Cobas and BRAHMS Kryptor); this is expected for the different technical principles on which the methods are based. PCT-D is a latex enhanced immunoturbidimetric assay, whereas PCT-BR is an electrochemiluminescent immunoassay and PCT-BK is a sandwich immunoassay using time-resolved amplified cryptate emission technology. It can be observed that for PCT-BR and PCT-BK, the between-day component of imprecision was negligible, whereas for the PCT-D, especially at lower concentrations, the between-day component was relevant. The observed LoD and the functional sensitivity for PCT-D were much higher than those declared by Diazyme (0.051 and 0.15 µg/L) [19], but in line with those published by Dipalo et al. [20], whereas for PCT-BR and PCT-BK, the values were slightly better than those declared [17, 18]. The reproducibility performances of PCT-BR at very low PCT concentrations are clearly superior to those of the other two systems (Figure 1). The results of the linearity experiment for PCT-D were not in line with the manufacturer's specifications neither with what obtained by Dipalo et al. [20]. Linearity was checked in two different experiments (same reagent lot) (see Supplemental Figure 1); moreover, the automatic dilution system of Roche for clinical chemistry assays (use of a reduced sample volume) was not successful (data not shown), so only manual dilutions with a negative serum were effective for samples with PCT concentration >25 µg/L. For PCT-BK the declared linearity limit was reached (43 µg/L was the last dilution under the limit of 50 µg/L for direct measuring range while for PCT-BR a good linearity was obtained up to the highest concentration tested (68.7 µg/L) that however is below the manufacturer's specifications (100 µg/L).

Method comparison

This part revealed unexpected results regarding PCT-D. It demonstrated a poor correlation to the reference (r = 0.44 when calculated on low concentration samples, up to 5 µg/L). The presence of a certain number of aberrant high results is evident in Figure 2A and even more when the data are presented as bias plot (Supplemental

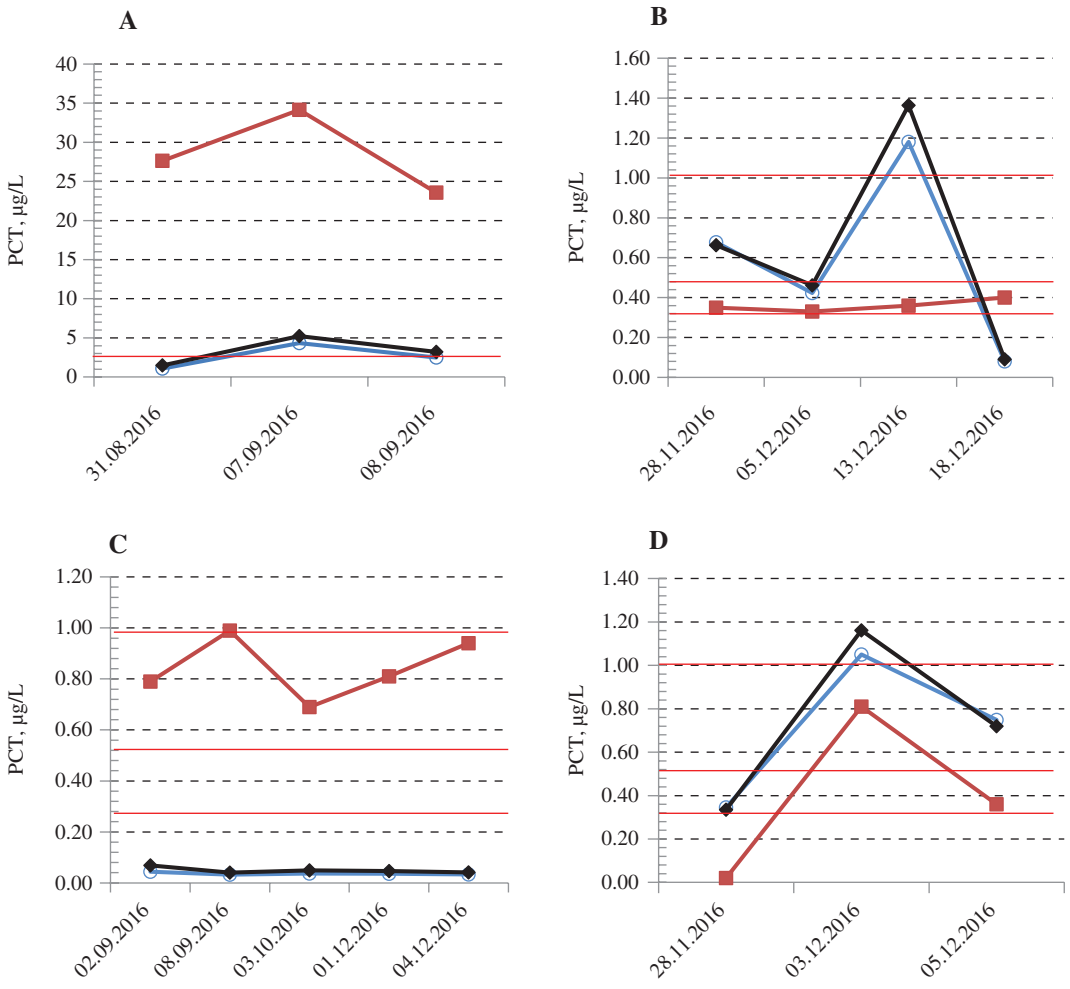

Figure 4: Time course of PCT values in four patients (A–D) with deviating results of PCT-D vs. PCT-BK/PCT-BR. --■-- PCT-D, --O-- PCT-BR, --◆-- PCT-BK, the red horizontal lines represent the clinical cutoffs.

Table 3: Frequency of discrepant samples (Y vs. X) and percent bias estimation.

	Deviation by more than 50%		Deviation by more than 30%		Average % bias	
	Number	%	Number	%	Mean	Median
Diazyme vs. BRAHMS Kryptor	143	59.8	202	84.5	229.6	−33.7
BRAHMS Roche vs. BRAHMS Kryptor	13	5.4	28	11.7	4.2	−0.7

Figure 2A). The lack of correlation at low PCT concentration is evident in Figure 2B that represents the results in the zone 0–1 µg/L. The assessment of deviating results and method bias is reported in Table 3. As summarized in Table 2, there was a high number of false-negative and false-positive results with the PCT-D, particularly for the lower cutoffs. The significant bias of PCT-D to the reference together with relatively high imprecision of the PCT-D, particularly at lower range, contributes to the low Cohen's κ-values reported in Table 2. To identify the different components that contribute to the poor correlation between PCT-D and PCT-BK, we plotted the % difference between the two methods vs. the PCT-BK values, focusing at the lower PCT concentration range (Figure 5).

It appears that a significant part of the differences at PCT concentrations <0.5 µg/L is explained by the high imprecision of the PCT-D, combined with the relevant calibration bias (–33.7%). However, almost 40% of the

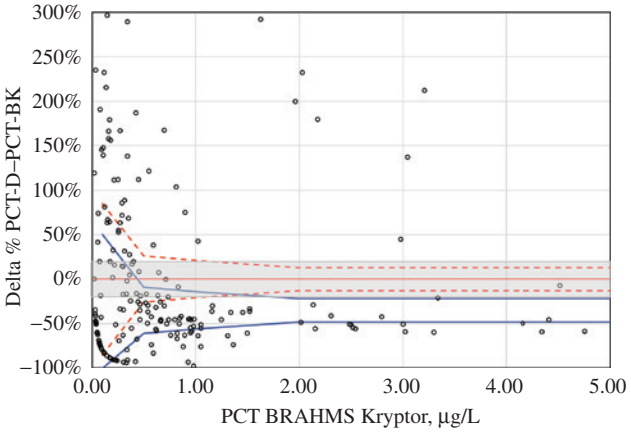

Figure 5: Percent differences between PCT-D and PCT-BK plotted vs. PCT-BK values.
The gray area indicates the acceptable total error. The red dotted lines delimitate the expected dispersion due only to the combined imprecision of the two methods (zero bias, two times the combined SD). The blue lines delimitate the expected dispersion considering combined imprecision and calibration bias (−33.7%).

samples at concentration <0.5 µg/L seem to show sample-related interferences (differences up to 26,000%, the y axis of Figure 5 is truncated at 300%). The same elaboration for PCT-BR (Supplemental Figure 3) shows that most of the samples are within the ±20% acceptable total error [21], and only values <0.25 µg/L present higher % differences.

The obtained results are only partially in contrast with those reported by Dipalo et al. [20]. In fact, looking carefully at the correlation plot in the low range, the dispersion was high; moreover, the reported κ-values at 0.25 and 0.50 µg/L were even lower (0.14 and 0.24, respectively) [20]. The authors focused more at higher cutoff for judging the level of agreement. In fact, they suggested the use of a confirmatory method for Diazyme results <0.26 µg/L. However, if following this concept and taking into account the very low performance also at cutoff 0.5 µg/L, as confirmed in our study, probably many more samples would need to be retested as in our practice nearly two third of all samples in clinical routine have PCT <0.5 µg/L.

The PCT-D has the advantage of being applicable to the common clinical chemistry analytical systems, providing results in a short time with potentially lower cost, but the obtained low concordance to the reference, as reflected by the κ-values for all four tested cutoffs, should cause caution in its use. The significant number of false negatives (Table 2) limits the use of PCT-D as a test for differential diagnosis or initiation of antibiotic therapy especially in patients with LRTI.

It is difficult to hypothesize the reasons for this different performance. Although the lower assay sensitivity in general can be attributed to the turbidimetric assay format, there seem to be also other aspects influencing the specific assay performance like calibration, blocking of interfering substances, etc., but potentially also the type of antibodies used, where, in contrast to the BRAHMS assay [22], no information is available for Diazyme.

This could also provide some explanation for the observation that PCT-D for some samples presented a response completely different from PCT-BK/PCT-BR. Further investigation would be required to understand the reason for the differing behavior of the PCT-D vs. the PCT-BR and PCT-BK.

Different to the PCT-D, the comparison between PCT-BR and PCT-BK shows, as expected by previously published data [23], a very good correlation as appears from the Figure 3A and B and from the level of agreement indicated in Table 2. The small underestimation of PCT-BR (slope 0.912), very similar to the one reported by the manufacturer [18], explains the <100% agreement between the two methods (see Tables 2 and 3). However, a high agreement of PCT-BR with PCT-BK was demonstrated for all analyzed cutoffs. Therefore, it can be concluded that PCT-BR can share the same cutoffs and clinical algorithms as established with PCT-BK. This is supported by the use of PCT-BR together with PCT-BK in a recently published randomized controlled interventional trial on PCT-guided antibiotics stewardship in critically ill patients using a clinical algorithm for discontinuation of antibiotics based of >80% decline of PCT and/or PCT <0.5 µg/L together with clinical improvement [7]. The extremely good precision of PCT-BR at low PCT concentration makes the method well suited for differential diagnosis and PCT-based guidance of antibiotic therapy both for patients with LRTI or high risk patients with suspected or confirmed systemic bacterial infection/sepsis [7–11].

Acknowledgments: We thank Dr. Andrej Schwabe, Biostatistician, Thermo Fisher Scientific, for the support in data elaboration and Thermo Fisher Scientific for donating us the reagents and for the financial support to the study.
Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: Thermo Fisher Scientific.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Meisner M. Update on procalcitonin measurements. Ann Lab Med 2014;34:263–73.
2. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis 2013;13:426–35.
3. Morgenthaler NG, Struck J, Fischer-Schulz C, Bergmann A. Sensitive immunoluminometric assay for the detection of procalcitonin. Clin Chem 2002;48:788–90.
4. Schuetz P, Bretscher C, Bernasconi L, Mueller B. Overview of procalcitonin assays and procalcitonin-guided protocols for the management of patients with infections and sepsis. Expert Rev Mol Diagn 2017;17:1–9.
5. Bouadma L, Luyt C-E, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010;375:463–74.
6. Hohn A, Schroeder S, Gehrt A, Bernhardt K, Bein B, Wegscheider K, et al. Procalcitonin-guided algorithm to reduce length of antibiotic therapy in patients with severe sepsis and septic shock. BMC Infect Dis 2013;13:158.
7. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis 2016;16:819–27.
8. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al. Effect of procalcitonin-based guidelines vs. standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. J Am Med Assoc 2009;302:1059–66.
9. Long W, Deng X, Zhang Y, Lu G, Xie J, Tang J. Procalcitonin guidance for reduction of antibiotic use in low-risk outpatients with community-acquired pneumonia. Respirology 2011;16:819–24.
10. Stockmann C, Ampofo K, Killpack J, Williams DJ, Edwards KM, Grijalva CG, et al. Procalcitonin accurately identifies hospitalized children with low risk of bacterial community-acquired pneumonia. J Pediatric Infect Dis Soc 2017. doi: 10.1093/jpids/piw091. [Epub ahead of print].
11. CLSI. Evaluation of precision of quantitative measurement procedures; Approved guideline – third edition. CLSI Document EP05-A3. Wayne, PA: Clinical and Laboratory Standards Institute. 2014.
12. CLSI. Evaluation of detection capability for clinical laboratory measurement procedures; Approved guidelines – second edition. CLSI document EP17-A2. Wayne, PA: Clinical Laboratory Standards Institute, 2012.
13. CLSI. Evaluation of the linearity of quantitative measurement procedures: a statistical approach; Approved guideline. CLSI document EP6-A. Wayne, PA: Clinical Laboratory Standards Institute, 2003.
14. R CT. R: a language and environment for statistical computing. [Internet]. Vienna, Austria: R Foundation for Statistical Computing, 2014. Available at http://www.r-project.org/. Accessed 21 Feb 2017.
15. Manuilova E, Schuetzenmeister A, Model F. mcr: Method Comparison Regression. R package version 1.2.1. [Internet]. 2014. Available at http://cran.r-project.org/package=mcr. Accessed 21 Feb 2017.
16. Passing H, Bablok W. A new biometrical procedure for testing the equality of measurements from two different analytical methods. Application of linear regression procedures for method comparison studies in clinical chemistry, Part I. J Clin Chem Clin Biochem 1983;21:709–20.
17. B · R · A · H · M · S PCT sensitive KRYPTOR – B · R · A · H · M · S PCT [Internet]. Available at http://www.procalcitonin.com/pct-assays/pct-sensitive-kryptor.html. Accessed 11 Feb 2017.
18. ELECSYS B · R · A · H · M · S PCT – B · R · A · H · M · S PCT [Internet]. Available at http://www.procalcitonin.com/pct-assays/pct-elecsys.html. Assessed Feb 11 2017.
19. Procalcitonin (PCT) Assay [Internet]. Available at http://www.diazyme.com/procalcitonin-pct-assay. Accessed 11 Feb 2017.
20. Dipalo M, Buonocore R, Gnocchi C, Picanza A, Aloe R, Lippi G. Analytical evaluation of Diazyme procalcitonin (PCT) latex-enhanced immunoturbidimetric assay on Beckman Coulter AU5800. Clin Chem Lab Med 2015;53:593–7.
21. Barassi A, Pallotti F, Melzi d'Eril G. Biological variation of procalcitonin in healthy individuals. Clin Chem 2004;50:1878.
22. Struck J, Strebelow M, Tietz S, Alonso C, Morgenthaler NG, Van Der Hoeven JG, et al. Method for the selective measurement of amino-terminal variants of procalcitonin. Clin Chem 2009;55:1672–9.
23. De Wolf HK, Gunnewiek JK, Berk Y, Van Den Ouweland J, De Metz M. Comparison of a new procalcitonin assay from Roche with the established method on the Brahms Kryptor. Clin Chem 2009;55:1043–4.

Supplemental Material: The online version of this article offers supplementary material (https://doi.org/10.1515/cclm-2017-0159).