Clin. Lab. 2021;67:XXX-XXX

LETTER TO THE EDITOR

Comparison of Automated Procalcitonin Immunoassays under Routine Conditions

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(Clin. Lab. 2021;67:xx-xx. DOI: 10.7754/Clin.Lab.2020.200457)

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KEY WORDS

procalcitonin, chemiluminiscence, turbidimetry, method comparison, sepsis, antibiotics

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Sepsis is a frequent condition in hospitalized patients with mortality rates between 25 and 30%. In 2013, German hospitals registered 279,530 sepsis cases and 67,849 of these patients died [1]. Early diagnosis and targeted therapy are key prognostic factors. Over the past 20 years, procalcitonin (PCT) testing has been established as an important pillar in the management of septic patients. Although its usefulness for the early diagnosis of sepsis is still a matter of debate, there is broad consensus that PCT is helpful in guiding antibiotic therapy [2]. In addition, PCT can aid the diagnosis of late-onset neonatal sepsis, bacterial meningitis, and other organ-related bacterial infections.

In healthy individuals, PCT is almost exclusively produced by the C cells of the thyroid gland and serum concentrations are low. However, under septic conditions, the calcitonin gene (CALC-1) is also expressed in many other tissues resulting in substantially higher serum concentrations [3]. According to literature and test manufacturers, PCT values below 0.5 ng/mL do not suggest a severe infection, while values above 2 ng/mL reflect a high probability for systemic inflammation due to sepsis [4].

For many years, commercial PCT tests were manufactured and distributed by a single supplier (B.R.A.H.M.S. GmbH, Henningsdorf, Germany). Therefore, most scientific data and clinical guidelines are based on results generated with this test. With the recent expiry of B.R.A.H.M.S. patent protection other assays have enter-

Letter to the Editor accepted May 25, 2020

Table 1. Characteristics of the compared PCT assays as promoted by the respective manufacturers.

	ECLIA	LETIA
Analyte	**procalcitonin (PCT)**	
Unit	**ng/mL**	
Test principle	**electrochemiluminescence immunoassay**	**latex-enhanced turbidimetric immunoassay**
Reagent product name (manufacturer)	**Elecsys Procalcitonin (B·R·A·H·M·S GmbH)**	**Diazyme Procalcitonin Assay (Diazyme Laboratories)**
Analyzer (manufacturer)	**cobas 8000 e602 (Roche Diagnostics)**	**cobas 8000 c701 (Roche Diagnostics)**
Used antibodies	**monoclonal anti-PCT (mouse)**	**anti-human PCT antibodies (species not mentioned)**
Limit of blank (LOB) Limit of detection (LOD) Limit of quantification (LOQ)	**not specified not specified 0.02**	**0.06 0.16 0.20**
Measurement range	**0.02 - 100.00**	**0.20 - 52.00**
Reference range	**≤ 0.046**	**0.02 - 0.30**
Clinical cutoffs	**≥ 0.5 ≥ 2 ≥ 10**	

All values are given in ng/mL.

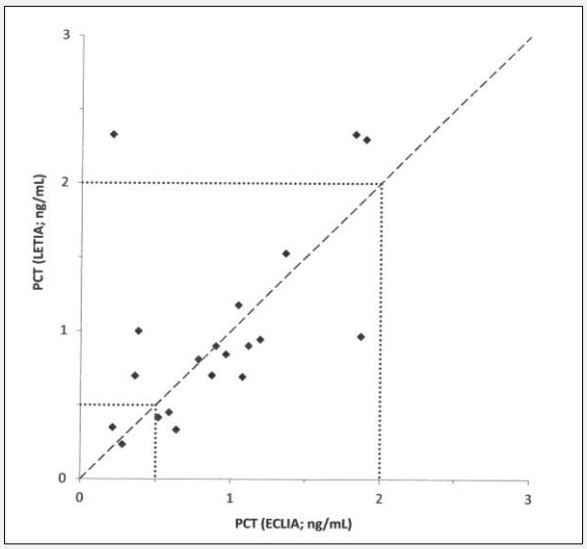

Figure 1. Scatterplot of PCT results obtained with ECLIA and LETIA.

Only samples containing between 0.2 ng/mL (measured with ECLIA and LETIA) and 2.0 ng/mL (measured with ECLIA) are displayed. The dashed line is the line of identity, the dotted lines mark the clinical cutoffs at 0.5 and 2.0 ng/mL.

ed the market. However, knowledge about the analytical and clinical performance of these novel PCT assays is limited. One of these novel PCT assays is manufactured by DIAZYME Laboratories, Inc. (Poway, CA, USA). Interestingly, the pack insert offers identical clinical cutoffs as B.R.A.H.M.S. suggesting a comparable ana-

lytical performance. However, in the absence of an international reference material and a reference method, a comparable performance of both assays is questionable. The two assays have substantially different test formats. B.R.A.H.M.S. employs a sandwich immunoassay format whereas the DIAZYME test is a latex-enhanced turbidimetric immunoassay (LETIA). B.R.A.H.M.S. has made its assay available to several manufacturers of integrated laboratory analyzers, such as Roche, Abbott or Diasorin, which use different detection methods on their instruments.

Laboratories that consider using the DIAZYME assay need to know the analytical and diagnostic performance of this assay. Therefore, we compared the ELECSYS B.R.A.H.M.S PCT test from Roche (Roche Diagnostics, Vienna, Austria) with the DIAZYME assay in 68 residual serum samples that where sent to our laboratory for PCT testing. From each patient only one sample was included in this comparison. While the ELECSYS B.R.A.H.M.S. PCT assay was applied on the e602 module of a cobas® 8000 analyzer (Roche Diagnostics), the DIAZYME test was installed on the c701 module of the same instrument. The performance characteristics claimed by the manufacturers of both tests are detailed in Table 1. All tests were completed within three hours after arrival of the samples in the laboratory. The two assays offer different limits of quantification (LOQs), which impedes the comparison of samples with a PCT concentration below the LOQ of at least one assay. Therefore, we excluded 15 pairs of results from statistical analyses. For the remaining 53 samples we obtained numerical results above the LOQs of both assays, which were used for statistical analyses.

Comparing the results of both assays using a Mann-Whitney-U test, did not reveal a significant difference ($p = 0.76$). In line with this observation, subsequent Passing-Bablok regression analysis did not show proportional (CI from 0.97 to 1.13) or constant (CI from -0.25 to 0.16) bias. The relationship between the two assays was linear (CUSUM test, $p = 0.99$). These results suggest good agreement of both tests. Based on the cut-offs provided by the manufacturers, 57 cases (84%) showed diagnostic agreement between the two tests. In the remaining 16% (11 cases) the results obtained with the two assays did not fall in the same category. Five of these cases had PCT concentrations within 20% of the respective cutoff and may thus be explained by the measurement uncertainties of both assays. In the remaining samples, diagnostic discrepancies were not explainable by assay imprecision. For two samples the results obtained with DIAZYME and B.R.A.H.M.S. differed enormously, 2.3 vs. 0.2 ng/mL and 10.6 vs. 2.9 ng/mL. Visual inspection and serial dilution experiments excluded common interferences, such as hemolysis, hyperbilirubinemia or heterophilic antibodies.

In an attempt to clarify, which result agrees better with the clinical status we accessed the medical records of all patients. Most patients were hospitalized in intensive care units, five of them due to sepsis. Sixty-one patients had anti-infectious therapy at the time of blood sampling. In 54% (n = 33) an infectious pathogen was identified with bacteria being more frequent (n = 30) than fungi or viruses. As expected, septic patients had higher mean values (DIAZYME = 42 ng/mL, B.R.A.H.M.S. = 45 ng/mL) than non-septic patients (DIAZYME = 6.8, B.R.A.H.M.S. = 6.9 ng/mL). In nine of the 11 cases with discrepant results, therapy would not have been different. Both patients with the two most discrepant pairs of results had antibiotic therapy, but never developed sepsis. The higher PCT result of the DIAZYME assay can probably cause a prolonged hospitalization and/or lead to an unnecessary switch of antibiotic treatment.

Taken together, despite different test formats and analytical capabilities (LOQ, measurement range) the results obtained with both assays agree in most cases. Nevertheless, in individual cases however, clinically significant discrepancies can occur with no clear explanation. At present, many laboratories still favor the B.R.A.H.M.S. assay because the diagnostic performance bases on many clinical studies. In addition, from a theoretical point of view, a turbidimetric immunoassay is more prone to interferences, such as hemolysis, lipidemia or immunocomplexes. However, in the absence of an acknowledged standard reference material and a reference measurement procedure accuracy cannot be judged. In any case, hospitals should always monitor their patients with the same assay as discrepancies can potentially be misleading. Future studies should focus on the diagnostic performance and clinical utility of the DIAZYME assay. In addition, the development of a standard reference material would be very helpful for the alignment of different PCT assays.

Declaration of Interest:
None.

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