VITROS Products Immunodiagnostic

INSTRUCTIONS FOR USE PCT

VITROS Immunodiagnostic Products B•R•A•H•M•S PCT Reagent Pack	REF	690 5558
VITROS Immunodiagnostic Products B•R•A•H•M•S PCT Calibrators	REF	690 5559

Intended Use

For *in vitro* diagnostic use only.

VITROS Immunodiagnostic Products B•R•A•H•M•S PCT Reagent Pack

For the quantitative measurement of procalcitonin (PCT) in human serum and plasma (lithium heparin and EDTA) using the VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated Systems.

The VITROS B•R•A•H•M•S PCT test is indicated as an aid to be used in conjunction with clinical evaluation for:

- the early detection and differential diagnosis of clinically relevant bacterial infections,
- the assessment of the degree of severity and the prognosis of the outcome of systemic bacterial infection, sepsis, severe sepsis and septic shock,
- identifying patients that benefit from antibiotic treatment,
- monitoring of antibiotic therapy within the measuring range,
- the assessment of successful antibiotic therapy in patients with suspected or confirmed bacterial infection.

VITROS Immunodiagnostic Products B•R•A•H•M•S PCT Calibrators

For use in the calibration of the VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated Systems for the quantitative measurement of procalcitonin (PCT) in human serum and plasma (lithium heparin and EDTA).

Summary and Explanation of the Test

Sepsis and its complications is a global healthcare problem, characterized by whole body inflammation in response to microbial infection, which may lead to organ dysfunction. [1, 2] The severity of sepsis correlates with mortality. [3- 7] Procalcitonin (PCT) is a peptide precursor for the hormone calcitonin, the latter being involved with calcium homeostasis. The prohormone has 116 amino acids and is comprised of the following regions: a 57-amino acid sequence at the amino terminus, the centrally positioned immature calcitonin that contains a terminal glycine; and a 21-amino acid calcitonin carboxyterminus peptide. [8] Calcitonin has a short half-life of 10 minutes while procalcitonin has a relatively longer half-life of 25 to 30 hours. [9] Procalcitonin is known to be produced by the parafollicular cells of the thyroid, but it is also secreted from neuroendocrine cells of the lung and intestine. The latter two sources of procalcitonin provide its true clinical utility, as they increase its production in response to a proinflammatory stimulus, particularly when the stimulus is of bacterial origin. [7, 10] In healthy people, plasma procalcitonin concentrations are found to be low. [11] Procalcitonin levels rise rapidly within 6–12 hours after an infectious bacterial insult. The magnitude of the increase in plasma procalcitonin concentration correlates with the severity of the bacterial infection with concentrations above defined cutoffs to indicate clinically relevant bacterial infection, requiring antibiotic treatment. [12] The relief of the septic infection is accompanied by a decrease in procalcitonin concentration which returns to normal within 24 hours. [13, 14] The continuous decline of procalcitonin is indicative of effective source control measures and has been used to guide safe discontinuation of antibiotic therapy. [15, 16] Also, low procalcitonin concentrations at predefined cutoffs can identify patients without clinically relevant bacterial infections; in these individuals antibiotic therapy can be safely discontinued. [12] Therefore measurement of procalcitonin concentrations may aid in the risk assessment of critically ill patients for progression to severe sepsis and septic shock and the change of procalcitonin levels over time may also offer information about the risk of mortality after diagnosis of severe sepsis or septic shock. [17, 18]

Principles of the Procedure

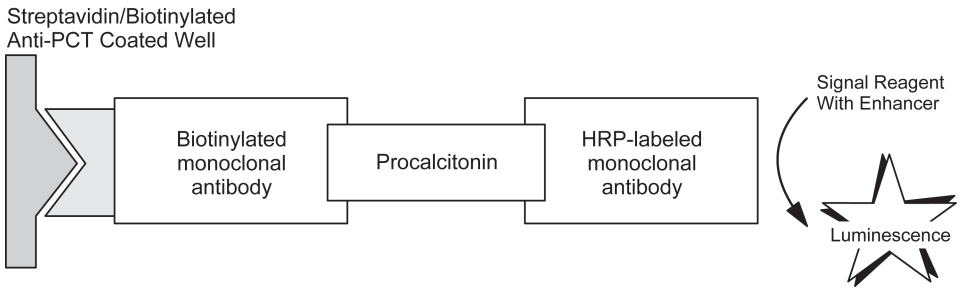
The VITROS B•R•A•H•M•S PCT test is performed using the VITROS B•R•A•H•M•S PCT Reagent Pack and the VITROS B•R•A•H•M•S PCT Calibrators on the VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated Systems using Intellicheck® Technology. A two-step immunometric technique is used, which involves the reaction of procalcitonin present in the sample with a biotinylated anti-procalcitonin antibody (rat monoclonal anti-procalcitonin) bound to streptavidin coated on a microwell in the first step. Unbound materials are removed by washing. The second step involves the reaction of antigen-antibody complex with a horseradish peroxidase (HRP)-labeled antibody conjugate (mouse monoclonal anti-procalcitonin). Unbound materials are removed by washing. The bound HRP conjugate

is measured by a luminescent reaction. [19] A reagent containing luminogenic substrates (a luminol derivative and a peracid salt) and an electron transfer agent, is added to the wells. The HRP in the bound conjugate catalyzes the oxidation of the luminol derivative, producing light. The electron transfer agent (a substituted acetanilide) increases the level of light produced and prolongs its emission. The light signals are read by the system. The amount of HRP conjugate bound is directly proportional to the concentration of procalcitonin present.

Test Type	System*	Incubation Time	Time to first result	Test Temperature	Reaction Sample Volume
Immunometric Immunoassay	ECi/ECiQ, 3600, 5600, XT 7600	13 minutes 20 seconds	24 minutes	37 °C	30 µL

* Not all products and systems are available in all countries.

Reaction Scheme



Warnings and Precautions

WARNING: Potentially Infectious Material

Use caution when handling material of human origin. Consider all samples potentially infectious. No test method can offer complete assurance that hepatitis B virus, hepatitis C virus (HCV), human immunodeficiency virus (HIV 1+2) or other infectious agents are absent. Handle, use, store and dispose of solid and liquid waste from samples and test components, in accordance with procedures defined by appropriate national biohazard safety guideline or regulation (e.g. CLSI document M29). [20]

WARNING: Contains ProClin 950 (CAS 2682-20-4) [21]

The VITROS B•R•A•H•M•S PCT Reagent Pack and VITROS B•R•A•H•M•S PCT Calibrators contain 0.5% and 0.466% ProClin 950 respectively. H317: May cause an allergic skin reaction. P280: Wear protective gloves. P302 + P352: IF ON SKIN: Wash with plenty of soap and water. P333 + P313: If skin irritation or rash occurs: Get medical advice/attention. P363: Wash contaminated clothing before reuse.

Refer to www.Orthoclinicaldiagnostics.com for the Safety Data Sheets and for Ortho contact information.

WARNING

Reagents

Reagent Pack Contents

1 reagent pack containing:

- 100 coated wells (rat monoclonal anti-procalcitonin antibody, 1.0 µg/mL)
- 10.20 mL assay reagent (buffer containing bovine gamma globulin, bovine serum albumin and antimicrobial agent)
- 13.10 mL conjugate reagent (HRP-conjugated mouse monoclonal procalcitonin antibody, 1.65 µg/mL in buffer with bovine serum albumin and antimicrobial agent)

Reagent Pack Handling

- The reagent pack is supplied ready for use.
- The reagent pack contains homogeneous liquid reagents that do not require shaking or mixing prior to loading onto the system.
- Handle the reagent pack with care. Avoid the following:
  - allowing condensation to form on the pack
  - causing reagents to foam
  - agitation of the pack

Reagent Pack Storage and Preparation

Reagent	Storage Condition		Stability
Unopened	Refrigerated	2–8 °C (36–46 °F)	expiration date
Opened	On system	System turned on	≤12 weeks
Opened	Refrigerated	2–8 °C (36–46 °F)	≤12 weeks

- The VITROS B•R•A•H•M•S PCT Reagent Pack is suitable for use until the expiration date on the carton when stored and handled as specified. Do not use beyond the expiration date.
- Do not freeze reagent packs.
- Load reagent packs directly from refrigerated storage to minimize condensation.
- Opened reagent packs are moisture/humidity sensitive. Store opened refrigerated reagent packs in a sealed VITROS Immunodiagnostic Products Reagent Pack Storage Box with desiccant.

Calibrator Contents

- 3 sets of VITROS B•R•A•H•M•S PCT Calibrators 1 and 2, 1.0 mL, procalcitonin in buffer with antimicrobial agent, nominal values 0.080 and 75.0 ng/mL (µg/L)
- Lot calibration card
- Protocol card
- 16 calibrator bar code labels (8 for each calibrator)

Calibrator Handling

- Use only with reagent packs of the same lot number. Mix thoroughly by inversion and bring to 15–30 °C (59–86 °F) before use. Each pack contains sufficient volume for a minimum of 6 determinations of each calibrator.
- Handle calibrators in original stoppered containers to avoid contamination and evaporation. To avoid evaporation, limit the amount of time calibrators are on the system. Refer to the operating instructions for your system. Return to 2–8 °C (36–46 °F) as soon as possible after use, or load only sufficient volume for a single determination.

Calibrator Storage and Preparation

Calibrator	Storage Condition		Stability
Unopened	Frozen	≤-20 °C (≤-4 °F)	expiration date
Opened	Refrigerated	2–8 °C (36–46 °F)	≤13 weeks
Opened	Frozen	≤-20 °C (≤-4 °F)	≤18 weeks

- VITROS B•R•A•H•M•S PCT Calibrators are supplied frozen.
- VITROS B•R•A•H•M•S PCT Calibrators are suitable for use until the expiration date on the carton when stored and handled as specified. Do not use beyond the expiration date.
- Opened calibrators may be stored frozen (with no more than 3 freeze-thaw cycles).
- The VITROS B•R•A•H•M•S PCT test uses 30 µL of calibrator for each determination. Transfer an aliquot of each calibrator into a sample container (taking account of the minimum fill volume of the container), which may be bar coded with the labels provided. For details on minimum fill volume of sample cups or containers, refer to the operating instructions for your system.

Specimen Collection, Preparation and Storage

Patient Preparation

No special patient preparation is necessary.

Specimens Recommended

- Serum
- Plasma (lithium heparin, EDTA)

Specimens Not Recommended

No specimen limitations were identified. Refer to the Limitations of the Procedure section.

Special Precautions

IMPORTANT:	Certain collection devices have been reported to affect other analytes and tests. [22] Owing to the variety of specimen collection devices available, Ortho Clinical Diagnostics is unable to provide a definitive statement on the performance of its products with these devices. Confirm that your collection devices are compatible with this test.

Specimen Collection and Preparation

- Collect specimens using standard procedures. [23]
- Follow the instructions provided with your collection device for use and processing of the sample. [24]
- Samples should be thoroughly separated from all cellular material. Failure to do so may lead to an erroneous result.
- The VITROS B•R•A•H•M•S PCT test uses 30 µL of sample for each determination. This does not take account of the minimum fill volume of the chosen sample container. For details on minimum fill volume of sample cups or containers, refer to the operating instructions for your system.

Handling and Storage Conditions

- Handle samples in stoppered containers to avoid contamination and evaporation.
- Follow procedures within your laboratory to avoid cross contamination of patient specimens.
- The amount of time samples are on the system prior to analysis should be limited to avoid evaporation. Refer to the operating instructions for your system.
- Return to 2–8 °C (36–46 °F) as soon as possible after use or load sufficient volume for a single determination.
- Serum and plasma samples may be stored for up to 24 hours at room temperature 15–30 °C (59–86 °F). Serum and plasma samples may be stored for up to 48 hours at 2–8 °C (36–46 °F).
- Samples that will not be tested within the time frames outlined above should be stored frozen at -20 °C (-4 °F). Serum and plasma samples tested initially and after 2 months of storage at -20 °C (-4 °F) showed no differences in clinical performance. Serum and plasma samples may be subjected to up to four freeze-thaw cycles.
- Thoroughly mix samples by inversion and bring to 15–30 °C (59–86 °F) before use.

Testing Procedure

Materials Provided

- VITROS Immunodiagnostic Products VITROS B•R•A•H•M•S PCT Reagent Pack
- VITROS Immunodiagnostic Products VITROS B•R•A•H•M•S PCT Calibrators

Materials Required but Not Provided

- VITROS Immunodiagnostic Products Signal Reagent
- VITROS Immunodiagnostic Products Universal Wash Reagent
- VITROS Immunodiagnostic Products High Sample Diluent B
- Quality control materials such as VITROS Immunodiagnostic Products VITROS B•R•A•H•M•S PCT Controls
- VITROS Immunodiagnostic Products Reagent Pack Storage Box (optional) with desiccant

Operating Instructions

Check the inventory regularly to aid the management of reagents and ensure that sufficient VITROS Signal Reagent, VITROS Universal Wash Reagent and calibrated reagent lots are available for the work planned. When performing panels of tests on a single sample, ensure that the sample volume is sufficient for the tests ordered.

Ensure sufficient VITROS High Sample Diluent B Reagent Pack is loaded onto the system before processing samples. Refer to the VITROS High Sample Diluent B Reagent Pack instructions for use.

For detailed information refer to the operating instructions for your system.

Note:	Do not use visibly damaged product.

Sample Dilution

Samples with concentrations greater than the measuring range may be automatically diluted on the system up to 10-fold (1 part sample with 9 parts diluent) by the VITROS Immunodiagnostic and VITROS Integrated Systems with the VITROS Immunodiagnostic Products High Sample Diluent B Reagent Pack prior to testing. Refer to the VITROS High Sample Diluent B Reagent Pack Instructions for Use.

Default Test Name

The default test name which will appear on patient reports is procalcitonin. The default short name that will appear on the test selection menus and laboratory reports is PCT. These defaults may be reconfigured, if required. For detailed information refer to the operating instructions for your system.

Calibration

Calibration Procedure

- Calibration is lot specific; reagent packs and calibrators are linked by lot number. Reagent packs from the same lot may use the same calibration.
- A Master Calibration (a dose response curve covering the full calibration range) is established for each new reagent lot. Concentrations for the linked lot of calibrators are determined from the Master Calibration.
- Ensure that the Master Calibration for each new reagent lot is available on your system.
- Process calibrators in the same manner as samples. Calibration need not be programmed if bar code labels are used; load the calibrators in any order, calibration will be initiated automatically.
- When the calibrators are processed the signal expected for each calibrator is compared against the actual signal obtained. The Master Calibration is then rescaled to reflect the differences between the actual and expected signals. The validity of this calibration curve is assessed against a range of quality parameters, and if acceptable, it is stored for use with any reagent pack of that lot.
- The quality of calibration cannot be completely described by a single parameter. The calibration report should be used in conjunction with acceptable control values to determine the validity of the calibration.
- Recalibration is required after a pre-determined calibration interval, or when a different reagent lot is loaded.
- Calibration results are assessed against a range of quality parameters. Failure to meet any of the defined quality parameter ranges will be coded in the calibration report. For actions to be taken following a failed calibration refer to the operating instructions for your system.

Refer to the operating instructions for your system for detailed instructions on the calibration process.

When to Calibrate

- Calibrate when the reagent pack and calibrator lot changes.
- Calibrate every 56 days.
- After specified service procedures have been performed.
- If quality control results are consistently outside of your acceptable range.

For additional information on when to calibrate, refer to the operating instructions for your system.

Traceability of Calibration

Calibration of the VITROS B•R•A•H•M•S PCT test is traceable to in-house reference calibrators, which have been value-assigned to correlate to B•R•A•H•M•S PCT sensitive KRYPTOR.

Calibration Model

A modified four parameter logistic curve fit function is used to construct the Master Calibration. The calibration process rescales the Master Calibration to establish a valid stored curve for the VITROS Immunodiagnostic and VITROS Integrated Systems.

Measuring (Reportable) Range

System	Measuring (Reportable) Range
ECi/ECiQ, 3600, 5600, XT 7600	0.030–100 ng/mL (0.030–100 µg/L)

Quality Control

Quality Control Material Selection

Controls containing suitable levels of procalcitonin are recommended for use with the VITROS Immunodiagnostic and VITROS Integrated Systems. The performance of commercial control fluids should be evaluated for compatibility with this test before they are used for quality control.

Control materials may show a difference when compared with other procalcitonin methods if they contain high concentrations of preservatives, stabilizers, or other nonphysiological additives, or otherwise depart from a true human sample matrix. Appropriate quality control value ranges must be established for all quality control materials used with the VITROS B•R•A•H•M•S PCT test.

Quality Control Procedure Recommendations

- Good laboratory practice requires that controls be processed to verify the performance of the test.
- Choose control levels that check the clinically relevant concentrations.
- To verify system performance, analyze control materials:
  - After calibration
  - If the system is turned off for more than 2 hours
  - After reloading reagent packs that have been removed from the MicroWell Supply and stored for later use
  - According to local regulations or at least once each day that the test is being performed
  - After specified service procedures are performed

If quality control procedures within your laboratory require more frequent use of controls, follow those procedures.

- Analyze quality control materials in the same manner as patient specimens.
- If control results fall outside your acceptable range, investigate the cause before deciding whether to report patient results.
- Refer to published guidelines for general quality control recommendations. [25]

For more detailed information, refer to the operating instructions for your system.

Quality Control Material Preparation and Storage

Refer to the manufacturer's product literature for preparation, storage, and stability information.

Results

Results are automatically calculated by the VITROS Immunodiagnostic and VITROS Integrated Systems.

Reporting Units and Unit Conversion

Conventional	Alternate
ng/mL (µg/L x 1)	µg/L (ng/mL x 1)

Limitations of the Procedure

Known Interferences

The VITROS B•R•A•H•M•S PCT test was evaluated for interference consistent with CLSI document EP07. [26] Commonly encountered substances were tested on three lots of reagents. Of the compounds tested, none was found to cause a bias of >10%. Refer to "Specificity" for a list of compounds tested that did not show interference.

Other Limitations

- Heterophilic antibodies in serum or plasma samples may cause interference in immunoassays. [27] These antibodies may be present in blood samples from individuals regularly exposed to animals or who have been treated with animal serum products. Results that are inconsistent with clinical observations indicate the need for additional testing.
- The VITROS B•R•A•H•M•S PCT test has no high dose hook effect up to a concentration of 5,000 ng/mL (5,000 µg/L).

Expected Values and Interpretation of Results

Expected Values:

It is recommended that each laboratory establish its own upper reference limit (URL) for the population it serves.
The VITROS B•R•A•H•M•S PCT URL was established using the upper 95th percentile of a population of samples acquired from one hundred fifty (150) self-reported healthy adults, including 79 female and 71 male subjects. The subjects ranged in age from 24 to 78 years old, with forty-six percent of the subjects ≥60 years of age.
Subjects were excluded if they met any of the following exclusion criteria:

- History of cancer, chronic hepatitis or cirrhosis, chemical pneumonitis, kidney dysfunction, or autoimmune disease
- Trauma, burns, major surgery, shock, hepatitis, pancreatitis, fungal infection, malaria, heat stroke, muscle injury, or heart attack in the last 3 months
- Current use of immunosuppression medication
- Antibiotics taken within the last month
- Pregnancy

The overall observed 95th percentile URL from 150 normal, healthy donor samples is 0.077 ng/mL as shown in the table below.

VITROS B•R•A•H•M•S PCT URL

Sample Type	Number of Subjects	95th Percentile URL ng/mL
Serum, lithium heparin plasma, EDTA plasma	150	0.077

Interpretation of Results:

The medical decision points indicated below may vary according to the clinical situation. PCT concentrations are elevated in clinically relevant bacterial infections and continue to rise with the increasing severity of the disease. However, as an expression of individually different immune responses and different clinical situations, the same focus of infection may be associated with varying individual elevations in PCT concentrations.
Therefore, clinicians should use the PCT results in conjunction with the patient's other laboratory findings and clinical signs and should interpret the PCT values in the context of the patient's clinical situation. The medical decision points are therefore given for guidance only.

1. Diagnosis of systemic bacterial infection/sepsis [28- 30]

PCT values may be useful for the early detection and differential diagnosis of clinically relevant bacterial infections, and in the assessment of the degree of severity and the prognosis of the outcome of systemic bacterial infection, sepsis, severe sepsis and septic shock. [28- 30] Systemic inflammatory response syndrome (SIRS), Sepsis, Severe Sepsis, and Septic Shock were categorized according to the criteria of the consensus conference of the American College of Chest Physicians/ Society of Critical Care Medicine. [31]

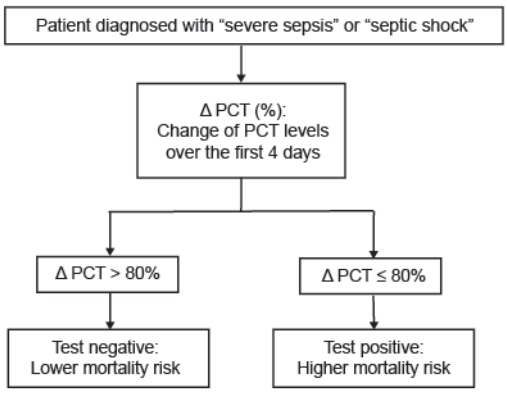
PCT Concentration (ng/mL or µg/L)	Interpretation of Results
<0.500	• Systemic infection (sepsis) is unlikely. • Local bacterial infection is possible. • Low risk for progression to severe systemic infection (severe sepsis). **CAUTION:** PCT levels below 0.500 ng/mL do not exclude an infection, because localized infections (without systemic signs) may be associated with such low levels. Also, if the PCT measurement is done very early after onset of infection (<6 hours), values may still be low. In this case, PCT should be re-assessed 6–24 hours later.
≥0.500 and ≤2.00	• Systemic infection (sepsis) is possible, but various conditions are also known to induce PCT. Refer to the Limitations - Interpretation section of these instructions for use for further information. • Moderate risk for progression to severe systemic infection (severe sepsis). The patient should be closely monitored both clinically and by re-assessing PCT within 6–24 hours.
>2.00 and <10.0	• Systemic infection (sepsis) is likely, unless other causes are known. Refer to the Limitations - Interpretation section of these instructions for use for further information. • High risk for progression to severe systemic infection (severe sepsis).
≥10.0	• Important systemic inflammatory response, almost exclusively due to severe bacterial sepsis or septic shock. • High likelihood of severe sepsis or septic shock.

2. Aid in the prediction of mortality in patients with severe sepsis and septic shock [18]

The change in PCT concentration over time provides information about the risk of mortality for patients diagnosed with severe sepsis or septic shock. [18]

- A PCT level that declines ≤80% from the day that severe sepsis or septic shock was clinically diagnosed (Day 0) to four days after clinical diagnosis (Day 4) is associated with higher cumulative 28-day risk of all-cause mortality than a decline >80%.
- The combination of the first PCT level (≤2.00 ng/mL or >2.00 ng/mL) at initial diagnosis of severe sepsis or septic shock with the patient's clinical course and the change in PCT level over time until Day 4 provides important additional information about the mortality risk.
- The PCT level on Day 1 (the day after severe sepsis or septic shock is first clinically diagnosed) can be used to calculate the percent change in PCT level at Day 4 if the Day 0 measurement is unavailable.
  Data support the classification of patients into higher and lower risk for mortality within 28 days according to the workflow below:

$$\Delta \text{ PCT} = \frac{\text{PCT}_{\text{Day 0 (or Day 1)}} - \text{PCT}_{\text{Day 4}}}{\text{PCT}_{\text{Day 0 (or Day 1)}}} \text{ X } 100\%$$



ΔPCT ≤80%

A decrease of PCT levels below or equal to 80% defines a positive ΔPCT test result representing a higher risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock.
If the PCT level increases over the first 4 days, the change in PCT result (ΔPCT) is interpreted as ΔPCT decline ≤80% and is defined a positive ΔPCT test result representing a higher risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock.

ΔPCT >80%

A decrease of PCT levels of more than 80% defines a negative ΔPCT result representing a lower risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock.

3. Differential Diagnosis of Lower Respiratory Tract Infections [16]

PCT values may be useful in differential diagnosis of Lower Respiratory Tract Infections (LRTI) and determining whether to initiate antibiotic treatment in patients with a differential diagnosis of lower respiratory tract infection. A summary of the findings of Schuetz at al. are presented in the table below.

PCT Concentration (ng/mL or µg/L)	Interpretation of Results
<0.100	• Bacterial infection very unlikely. Use of antibiotics is strongly discouraged, even in the presence of impaired pulmonary reserve in acute exacerbations of chronic obstructive pulmonary disease (AECOPD).
0.100 to 0.250	• Bacterial infection unlikely. The use of antibiotics is discouraged.
0.251 to 0.500	• Bacterial infection likely. Antibiotic treatment is recommended.
>0.500	• Bacterial infection very likely. Antibiotic treatment strongly recommended.

4. Antibiotic guidance in sepsis[32] and LRTI[33]

Antibiotic therapy should be considered regardless of PCT result if the patient is clinically unstable, is at high risk for adverse outcome, has strong evidence of bacterial pathogen, or the clinical context indicates antibiotic therapy is warranted. If antibiotics are withheld, reassess if symptoms persist/worsen and/or repeat PCT measurement within 6–24 hours.

In order to assess treatment success and to support a decision to discontinue antibiotic therapy, follow up samples should be tested once every 1–2 days, based upon physician discretion taking into account the patient's evolution and progress. Antibiotic therapy may be adjusted using the discontinuation formula below:

- PCT_{Peak}: Highest observed PCT concentration
- $PCT_{Current}$: Most recent PCT concentration
- ΔPCT: Change in PCT concentration
- ΔPCT: Calculate by using the following equation:

$$\Delta PCT = \frac{PCT_{Peak} - PCT_{Current}}{PCT_{Peak}} \times 100\%$$

Antibiotic therapy may be discontinued if the ΔPCT >80% or if the $PCT_{Current}$ is

- ≤0.250 ng/mL for LRTI patients.
- ≤0.500 ng/mL for suspected or confirmed septic patients.

Antibiotic therapy may be continued based upon other clinical findings, such as:

- apparent progression on chest x-ray or ongoing/increasing toxicity for LRTI patients or
- failure to control a local infection, or ongoing physiologic instability for patients with suspected or confirmed sepsis.

Caution:	If clinical picture has not improved and PCT remains high, re-evaluate and consider treatment failure or other causes.

Limitations - Interpretation [12, 34-37]

- VITROS B•R•A•H•M•S PCT is not indicated to be used as a stand-alone diagnostic test and should be used in conjunction with clinical signs and symptoms of infection and other diagnostic evidence. In cases where the laboratory results do not agree with the clinical picture or history, additional tests should be performed.
- Decisions regarding antibiotic therapy should NOT be based solely on procalcitonin concentrations.
- PCT results should always be interpreted in the context of the clinical status of the patient and other laboratory results.
- Changes in PCT levels for the prediction of mortality, and overall mortality, are strongly dependent on many factors, including pre-existing patient risk factors and clinical course.
- The need to continue Intensive Care Unit (ICU) care at Day 4 and other covariates (e.g., age and Sequential Organ Failure Assessment (SOFA) score) are also significant predictors of 28-day cumulative mortality risk.
- The safety and performance of PCT-guided therapy for individuals younger than age 18 years, pregnant women, immunocompromised individuals or those on immunomodulatory agents, was not formally analyzed in the supportive clinical trials.
- Severity of renal failure or insufficiency, may influence procalcitonin values and should be considered as potentially confounding clinical factors when interpreting PCT values. [12]

Increased PCT levels may not always be related to systemic infection. [34 - 36] Patients with increased PCT levels due to other conditions include, but are not limited to:

- Patients experiencing major trauma and/or recent surgical procedure including extracorporeal circulation or burns;
- Patients under treatment with OKT3 antibodies, OK-432, interleukins, TNF-alpha and other drugs stimulating the release of pro-inflammatory cytokines or resulting in anaphylaxis;
- Patients diagnosed with active medullary C-cell carcinoma, small cell lung carcinoma, or bronchial carcinoid;
- Patients with acute or chronic viral hepatitis and/or decompensated severe liver cirrhosis (Child-Pugh Class C);
- Patients with prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies or after resuscitation from cardiac arrest;
- Patients receiving peritoneal dialysis or hemodialysis treatment;
- Patients with biliary pancreatitis, chemical pneumonitis or heat stroke;
- Patients with invasive fungal infections (e.g. candidiasis, aspergillosis) or acute attacks of plasmodium falciparum malaria;
- Patients with Kawasaki, Still's Disease or Bell's Palsy;

- Patients with mushroom poisoning; and
- Neonates during the first 2 days of life.

Low PCT levels do not automatically exclude the presence of bacterial infection. Such low levels may be obtained, e.g., during the early course of infections, in localized infections and in subacute endocarditis. PCT levels may not be elevated in patients infected by certain atypical pathogens, such as Chlamydophila pneumoniae and Mycoplasma pneumoniae. [37] Therefore, follow-up and re-evaluation of PCT in clinical suspicion of infection is pivotal. The PCT measuring technique should be chosen dependent on intended clinical use.

Performance Characteristics

Clinical Performance Characteristics

Concordance Analysis

Concordance data between the VITROS B•R•A•H•M•S PCT and the B•R•A•H•M•S PCT sensitive KRYPTOR tests were obtained from the clinical performance study (n=2168) at the clinical decision points.

Clinical Decision Point (ng/mL)	Positive Agreement % (95% CI)	Negative Agreement % (95% CI)	Total Agreement (%)	Cohen's Kappa
0.100	98.9 (98.4–99.3)	86.1 (75.9–93.1)	98.5	0.772
0.250	99.1 (98.5–99.5)	91.8 (88.3–94.6)	98.0	0.917
0.500	99.2 (98.6–99.6)	91.9 (89.3–94.1)	97.4	0.926
2.00	99.4 (98.8–99.8)	96.0 (94.6–97.1)	97.8	0.955
10.0	97.1 (95.4–98.3)	98.4 (97.6–99.0)	98.0	0.949

Assessment of the degree of severity and the prognosis of the outcome of systemic bacterial infection, sepsis, severe sepsis and septic shock

The VITROS B•R•A•H•M•S PCT test was evaluated for the prediction of cumulative 28-day all-cause mortality using retrospective samples from a study of 858 adult patients diagnosed with severe sepsis or septic shock recruited across 13 investigational sites in the United States. The analysis population (598 subjects) included 44% female and 56% male patients with a mean age of 64 years. About half of the patients had severe sepsis (51%) versus septic shock (49%). Infections were mainly community acquired (91%). [18]
The binary test result (ΔPCT decline >80% or ≤80%) was significantly associated with 28-day cumulative mortality (vital status on day 28). The two-sided Fisher's exact test p-value was 0.006. Adjusted for Intensive Care Unit (ICU) versus non-ICU patient subgroups (based on hospital location at Day 4 after initial diagnosis), the association remained significant (Cochran-Mantel-Haenszel test p-value=0.026). In each binary ΔPCT subgroup, the 28-day cumulative mortality rate was stratified by need to continue ICU care on Day 4 and the selection of Day 0 vs. Day 1 as the baseline measurement day for the ΔPCT calculation:

28-Day Mortality Risk Stratified by Patient Location on Day 4: ΔPCT Decline >80% = Test Negative; ΔPCT Decline ≤80% = Test Positive					
ΔPCT Interval	Day 4 Patient Location	28-Day Mortality (%)		Prognostic Accuracy* (%)	
		ΔPCT Decline >80% (95% CI)	ΔPCT Decline ≤80% (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Day 0 to Day 4	ICU	21.1 (11.6–30.6)	29.6 (23.0–36.3)	77.5 (67.4–87.6)	31.4 (24.5–38.3)
	Non-ICU	5.4 (1.5–9.3)	11.0 (6.6–15.4)	74.6 (58.2–91.1)	42.3 (36.2–48.4)
Day 1 to Day 4	ICU	21.0 (11.7–30.3)	29.8 (23.1–36.4)	77.2 (67.0–87.3)	32.1 (25.2–39.0)
	Non-ICU	6.1 (1.7–10.5)	10.2 (6.1–14.3)	74.8 (58.5–91.2)	37.2 (31.3–43.1)

* Prognostic accuracy refers to how accurate the ΔPCT (decline ≤80% vs. >80%) can predict mortality risk.

Additional stratification of patients based on absolute initial PCT values (>2.00 ng/mL or ≤2.00 ng/mL) at Day 0 (or Day 1) revealed subgroups with particularly reduced or elevated mortality risk considering their patient location on Day 4. Mortality risk and prognostic performance are given for the following subgroups in the tables below:

1. Patients with PCT >2.00 ng/mL at Day 0 (or Day 1) receiving ICU care on Day 4
2. Patients with PCT ≤2.00 ng/mL at Day 0 (or Day 1) receiving ICU care on Day 4
3. Patients with PCT >2.00 ng/mL at Day 0 (or Day 1) without ICU care on Day 4
4. Patients with PCT ≤2.00 ng/mL at Day 0 (or Day 1) without ICU care on Day 4

28-Day Mortality Risk Stratified by Patient Location on Day 4, Absolute Initial PCT Value on Day 0: ΔPCT Decline >80% = Test Negative; ΔPCT Decline ≤80% = Test Positive						
ΔPCT Interval	Day 4 Patient Location	Initial PCT Value at Day 0 (ng/mL)	28-Day Mortality (%)		Prognostic Accuracy* (%)	
			ΔPCT Decline >80% (95% CI)	ΔPCT Decline ≤80% (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Day 0 to Day 4	ICU	≤2.00	5.5 (0.0–27.0)	23.7 (13.9–33.4)	97.7 (88.5–100.0)	10.3 (2.0–18.7)
		>2.00	22.7 (12.6–32.7)	33.7 (24.9–42.6)	70.5 (57.9–83.1)	42.1 (33.2–51.0)
	Non-ICU	≤2.00	5.0 (0.0–14.8)	8.3 (3.4–13.3)	90.9 (73.9–100.0)	14.7 (7.8–21.6)
		>2.00	5.5 (1.2–9.8)	15.1 (6.9–23.3)	64.6 (41.4–87.9)	62.6 (54.7–70.5)

* Prognostic accuracy refers to how accurate the ΔPCT (decline ≤80% vs. >80%) can predict mortality risk.

28-Day Mortality Risk Stratified by Patient Location on Day 4, Absolute Initial PCT Value on Day 1: ΔPCT Decline >80% = Test Negative; ΔPCT Decline ≤80% = Test Positive						
ΔPCT Interval	Day 4 Patient Location	Initial PCT Value at Day 1 ng/mL	28-Day Mortality (%)		Prognostic Accuracy* (%)	
			ΔPCT Decline >80% (95% CI)	ΔPCT Decline ≤80% (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Day 1 to Day 4	ICU	≤2.00	22.9 (0.0–61.0)	21.3 (11.4–31.1)	92.0 (77.6–100.0)	7.4 (0.0–15.1)
		>2.00	20.9 (11.3–30.4)	34.6 (26.0–43.3)	73.0 (60.9–85.1)	42.7 (33.9–51.4)
	Non-ICU	≤2.00	0.0 (0.0–20.6**)	7.2 (2.7–11.8)	100.0 (66.4**–100.0)	11.9 (5.8–17.9)
		>2.00	7.0 (2.0–12.0)	14.8 (7.0–22.6)	63.0 (40.9–85.1)	57.5 (49.2–65.8)

* Prognostic accuracy refers to how accurate the ΔPCT (decline ≤80% vs. >80%) can predict mortality risk.

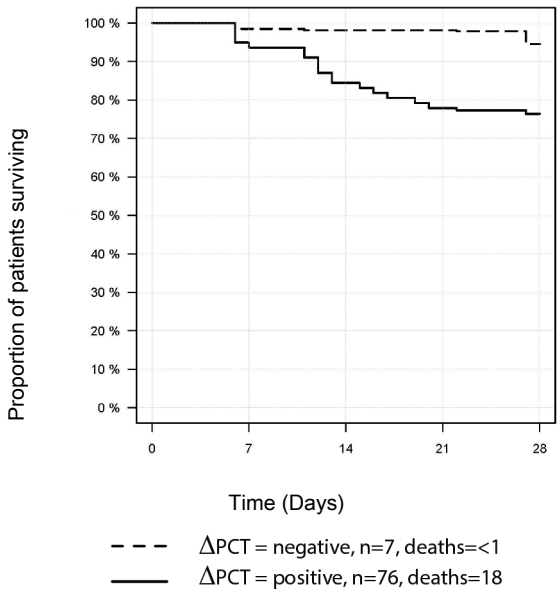
** Normality approximation of within-imputation variance not valid, therefore the estimate corresponds to within-imputation variation based on exact confidence intervals. [38]

The relative mortality ratios for ΔPCT positive (decline ≤80%) versus ΔPCT negative (decline >80%) patient subgroups were:

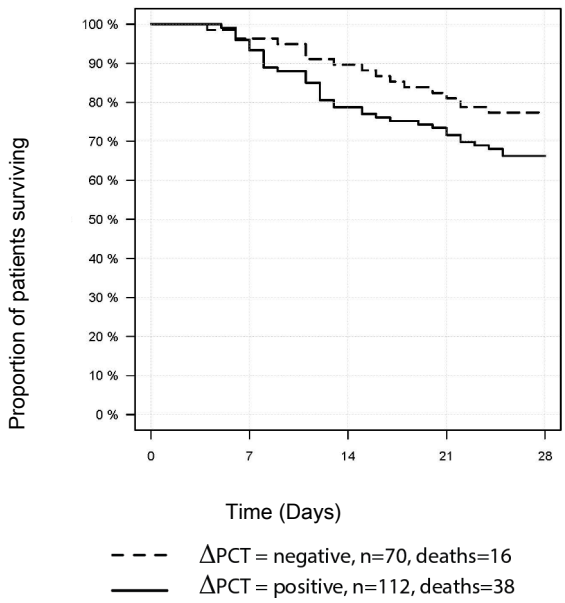
1.48 for patients with PCT >2.00 ng/mL at Day 0 receiving ICU care on Day 4
4.31 for patients with PCT ≤2.00 ng/mL at Day 0 receiving ICU care on Day 4
2.74 for patients with PCT >2.00 ng/mL at Day 0 without ICU care on Day 4
1.66 for patients with PCT ≤2.00 ng/mL at Day 0 without ICU care on Day 4
Based on relative mortality ratios, a decrease in PCT concentration by ≤80% from Day 0 (or Day 1) to Day 4 constitutes a higher risk for mortality within 28 days compared to >80% decreases in each subgroup.

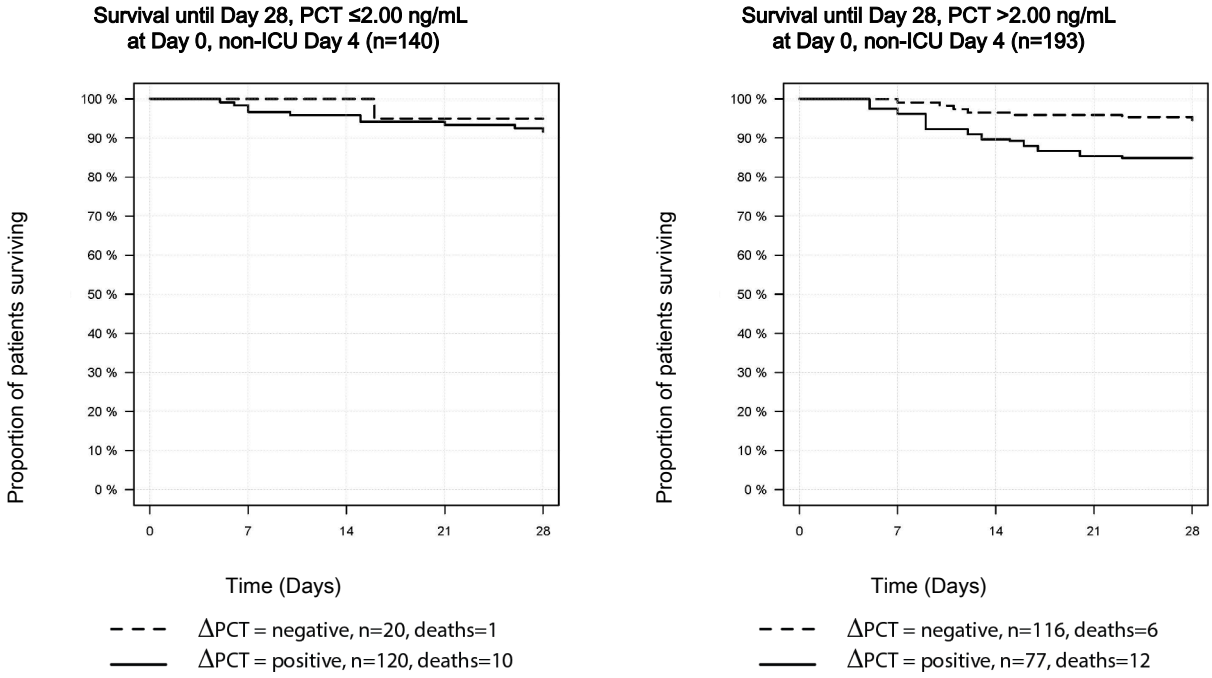
Time-to-event analyses, illustrated by the Kaplan-Meier curves below, demonstrate that patients had a lower survival probability (higher cumulative mortality risk) from study Day 4 until the end of follow-up time (Day 28) when the ΔPCT test result was positive compared to when the ΔPCT result was negative in all patient subgroups according to patient location on Day 4 and initial PCT value.

Survival until Day 28, PCT ≤2.00 ng/mL at Day 0, ICU Day 4 (n=83)



Survival until Day 28, PCT >2.00 ng/mL at Day 0, ICU Day 4 (n=182)





For the prediction of absolute mortality risks, patient location on Day 4 and initial PCT value should be considered:

- An initial PCT level ≤2.00 ng/mL on Day 0 followed by a PCT decline of more than 80% by Day 4 indicates a 4-fold lower cumulative 28-day mortality risk (5.5%) for patients with severe sepsis or septic shock who are still in the ICU by Day 4 compared to those patients with an initial PCT value >2.00 ng/mL (22.7%). Regardless of the initial PCT value, patients in the ICU on Day 4 that do not have more than an 80% decline in PCT plasma value from Day 0 to Day 4 have an even higher mortality risk of 23.7%–33.7%.
- An initial PCT value >2.00 ng/mL that does not decline by more than 80% by Day 4 signals that such patients remain at high mortality risk (15.1%) even when they are no longer receiving ICU care on Day 4. Mortality was otherwise observed between 5.0% to 8.3% for patients discharged from the ICU by Day 4.

A ΔPCT from Day 0 to Day 4 (decline ≤80% versus decline >80%) as a prognostic for 28-day cumulative risk of mortality was quantified by Cox proportional hazards regression analysis with a hazard ratio of 1.93 (95% CI of 1.19–3.12; p-value=0.008). The relative risk of cumulative 28-day mortality is about 2-fold higher if an individual tests positive for ΔPCT (decline ≤80%) than if an individual tests negative (decline >80%).
As a comparison, the table below lists the univariate hazard ratios for other clinical factors evaluated as separate predictors of mortality in the study population.

Predictors	Comparison	Hazard Ratio	95% CI	p-Value
ΔPCT (Day 0 to Day 4)	Decline ≤80% vs. >80%	1.93	1.19–3.12	0.008
ΔPCT (Day 1 to Day 4)	Decline ≤80% vs. >80%	1.73	1.07–2.79	0.025
APACHE* on Day 1	Difference of 5 units	1.36	1.22–1.53	<0.001
Maximum SOFA* of Day 0–Day 4	Difference of 3 units	1.73	1.50–2.00	<0.001
Antibiotic Adequacy	No vs. Yes	1.59	1.00–2.53	0.051
Sepsis Severity	Septic Shock vs. Severe Sepsis	1.19	0.80–1.76	0.386
Biological Infection Type	Gram Positive vs. Gram Negative	0.83	0.48–1.45	0.522
Biological Infection Type	Other vs. Gram Negative	0.99	0.63–1.54	0.960
Biological Infection Type	Fungal vs. Gram Negative	2.44	0.87–6.84	0.090
Clinical Infection Type	Nosocomial vs. Community Acquired	0.76	0.35–1.64	0.481
Positive Blood Culture	Yes vs. No	1.05	0.69–1.58	0.834
PCT on Day 0	>2.00 ng/mL vs. ≤2.00 ng/mL	1.39	0.90–2.15	0.139
Age	Difference of 5 years	1.16	1.08–1.24	<0.001
Gender	Male vs. Female	0.95	0.64–1.40	0.782
ICU Care on Day 4	Yes vs. No	3.45	2.24–5.31	<0.001

* APACHE: Acute Physiology, Age and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment

A ΔPCT from Day 0 (or Day 1) to Day 4 remains a prognostic parameter for the risk of cumulative 28-day mortality in patients diagnosed with severe sepsis or septic shock even when the hazard ratio is adjusted for other mortality predictors in Cox multiple regression models. The relative mortality risk estimates for ΔPCT and selected predictors are presented below with 95% confidence intervals. For continuous predictors, the hazard ratio (HR) was calculated for one standard deviation (SD) change in the predictor. For binary predictors, the risk estimate compares the hazards for the two binary results.

Model		Hazard Ratio (HR) (95% Confidence Interval)				
		Binary Predictors		Continuous Predictors (HR per 1 SD)		
ΔPCT Interval	Score + Covariates*	ΔPCT Decline (≤80% vs. >80%)	Day 4 Patient Location (ICU vs. Non-ICU)	APACHE (1 SD=8.13)	Maximum SOFA (1 SD=3.98)	Age (1 SD=16.18)
Day 0 to Day 4	APACHE	1.75 (1.00–3.04)	2.63 (1.64–4.21)	1.24 (0.99–1.56)	N/A	1.58 (1.26–1.98)
	Maximum SOFA	1.59 (0.92–2.73)	1.68 (1.02–2.78)	N/A	1.96 (1.53–2.52)	1.68 (1.35–2.10)
Day 1 to Day 4	APACHE	1.67 (0.99–2.82)	2.65 (1.65–4.24)	1.29 (1.03–1.61)	N/A	1.57 (1.25–1.96)
	Maximum SOFA	1.48 (0.88–2.51)	1.73 (1.05–2.84)	N/A	1.98 (1.54–2.54)	1.67 (1.34–2.09)

* The models also included the following predictors (hazard ratio results not shown): antibiotic adequacy, sepsis severity, biological infection type, clinical infection type, positive blood culture, PCT value on Day 0, gender. In the analysis, missing values for predictors were multiple imputed assuming they were Missing at Random (MAR), with the multiple imputations combined according to Rubin's rules. [39]

The change of PCT over time can also be described by the ratio of PCT values from Day 4 and Day 0 (or Day 1):

$$PCT_{ratio} = \frac{PCT_{Day\ 4}}{PCT_{Day\ 0\ (or\ Day\ 1)}}$$

A decline of ΔPCT=80% translates into a PCT ratio of 0.2. The PCT ratio has values larger than 0.2 when the ΔPCT decline is less than 80%, which is associated with a higher risk for cumulative 28-day all-cause mortality in patients diagnosed with severe sepsis or septic shock. Likewise, a PCT ratio below 0.2 indicates a lower risk for mortality within 28 days. On a continuous scale, the relative mortality risk for such patients is higher the larger the PCT ratio. The following table lists the hazard ratios for an increase by the factor 2 in PCT ratio (i.e., the relative increase in mortality risk for a

patient with any given PCT ratio compared to a patient with a 2-fold lower PCT ratio). For the patient location at Day 4, the risk estimate compares the hazards for patients with versus without ICU care on Day 4.

Model		Hazard Ratio (HR) (95% Confidence Interval)				
		Continuous Predictors (HR per 2-fold increase in PCT ratio or per equivalent in SD)				Binary Predictor
ΔPCT Interval	Score + Covariates*	PCT ratio (2-fold increase)	APACHE (SD equivalent)**	Maximum SOFA (SD equivalent)**	Age (SD equivalent)**	Day 4 Patient Location (ICU vs. Non-ICU)
Day 0 to Day 4	APACHE	1.29 (1.13–1.47)	1.08 (0.95–1.23)	N/A	1.32 (1.16–1.49)	2.52 (1.56–4.06)
	Maximum SOFA	1.21 (1.06–1.38)	N/A	1.40 (1.21–1.61)	1.35 (1.19–1.53)	1.68 (1.02–2.76)
Day 1 to Day 4	APACHE	1.40 (1.18–1.66)	1.20 (1.01–1.43)	N/A	1.44 (1.21–1.71)	2.60 (1.62–4.16)
	Maximum SOFA	1.33 (1.11–1.59)	N/A	1.65 (1.36–2.00)	1.51 (1.27–1.79)	1.75 (1.07–2.88)

* The models also included the following predictors (hazard ratio results not shown): antibiotic adequacy, sepsis severity, biological infection type, clinical infection type, positive blood culture, PCT on Day 0, and gender. In the analysis, missing values for predictors were multiple imputed assuming they were Missing at Random (MAR), with the multiple imputations combined according to Rubin's rules. [39]

** A unit change of ΔPCT on log-2-scale corresponded to 0.56 SD of ΔPCT from Day 0 until Day 4 (0.78 SD for ΔPCT from Day 1 until Day 4). Accordingly, the reported ΔPCT hazard ratios refer to an increase of ΔPCT by a factor of 2. For comparability, hazard ratios of the other continuous predictors were estimated for the same fractional SD (i.e., 0.56 or 0.78, respectively).

Cumulative 28-day all-cause mortality did not differ significantly for male versus female patients (Chi-square with Yates correction p-value=0.84). Demographics with outcome information are presented below:

Variable	Class	All Patients (N=598)	Dead (n)	Alive (n)	Mortality (%)
Gender	Female	264	46	218	17.4
	Male	334	55	279	16.5
Age (Years)	≤30	39	1	38	2.6
	>30 to 45	45	4	41	8.9
	>45 to 55	74	8	66	10.8
	>55 to 65	149	26	123	17.4
	>65 to 75	125	21	104	16.8
	>75	166	41	125	24.7
Ethnicity	African-American	202	32	170	15.8
	Asian	7	0	7	0.0
	Caucasian	362	64	298	17.7
	Hispanic	23	5	18	21.7
	Other	4	0	4	0.0
PCT on Day 0 (ng/mL)	<0.500	102	16	86	15.7
	≥0.500 to ≤2.00	98	13	85	13.3
	>2.00	342	67	275	19.6
	Missing	56	5	51	8.9

Limit of Detection

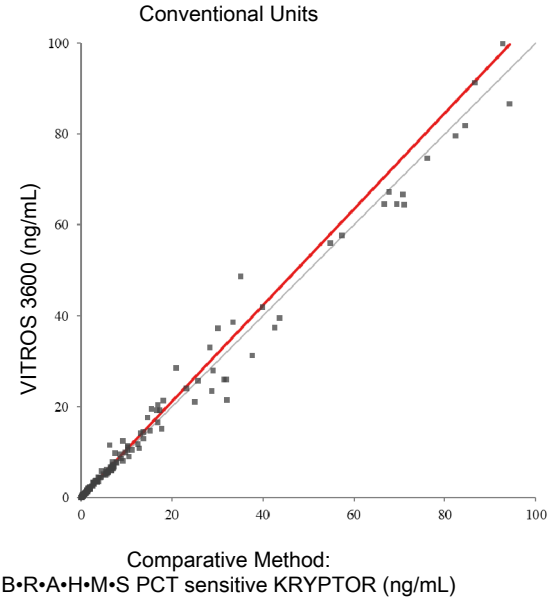
The Limit of Detection (LoD) for the VITROS B•R•A•H•M•S PCT test is 0.007 ng/mL (0.007 µg/L), determined consistent with CLSI document EP17. [40] The Limit of Quantitation (LoQ) was determined consistent with CLSI document EP17. [40] The observed Limit of Quantitation at 20% CV was determined to be 0.013 ng/mL (0.013 µg/L) and the claimed LoQ was set at 0.030 ng/mL (0.030 µg/L).

Limit of Detection and Limit of Quantitation

LoD		LoQ	
ng/mL	µg/L	ng/mL	µg/L
0.007	0.007	0.030	0.030

Accuracy (Method Comparison)

Accuracy was evaluated consistent with CLSI document EP09. [41] The plot and table show the results of a method comparison study using patient samples analyzed on the VITROS 3600 Immunodiagnostic System compared with those analyzed using the B•R•A•H•M•S PCT sensitive KRYPTOR test. The relationship between the 2 methods was determined by Weighted Deming [42] regression.



System	n	Slope	Correlation Coefficient	Conventional Units (ng/mL) = Alternate Units (µg/L)*	
				Range of Samples	Intercept
VITROS 3600 vs. Comparative Method	246	1.057	0.994	0.031–99.8	-0.010
VITROS ECi/ECiQ vs. VITROS 3600	244	0.964	1.000	0.032–93.3	0.006
VITROS 5600 vs. VITROS 3600**	242	0.984	0.999	0.030–97.9	-0.001

* The alternate units are 1.00 ng/mL=1.00 µg/L.

** Performance characteristics for the VITROS 5600 System are applicable to the VITROS XT 7600 System.

Precision

Precision was evaluated consistent with CLSI document EP05.[43] Two replicates each of seven patient pools and three controls were tested on two separate occasions per day on at least 20 different test days. The experiment was performed using three reagent lots on one VITROS ECi/ECiQ Immunodiagnostic System, one VITROS 3600 Immunodiagnostic System, and one VITROS 5600 Integrated System. Representative performance data are shown below.

VITROS System	Units = ng/mL (µg/L)							No. Observations	No. Days
	Mean B•R•A•H•M•S PCT Conc.	Within-run*		Within-cal**		Within-lab***			
		SD	%CV	SD	%CV	SD	%CV		
ECi/ECiQ	0.049	0.0014	2.8	0.0018	3.7	0.0019	3.9	80	20
	0.100	0.0031	3.1	0.0036	3.6	0.0039	3.9	80	20
	0.239	0.0042	1.8	0.0055	2.3	0.0077	3.2	80	20
	0.472	0.0073	1.6	0.0113	2.4	0.0162	3.4	80	20
	1.81	0.034	1.9	0.053	3.0	0.068	3.7	80	20
	27.0	0.54	2.0	0.89	3.3	1.13	4.1	80	20
	76.7	1.67	2.2	1.94	2.6	2.62	3.4	80	20
	0.463	0.0097	2.1	0.0143	3.1	0.0140	3.0	80	20
	1.79	0.029	1.6	0.040	2.2	0.061	3.4	80	20
	53.9	0.93	1.7	1.38	2.6	2.01	3.7	80	20
3600	0.041	0.0006	1.4	0.0018	4.3	0.0025	6.4	80	20
	0.096	0.0010	1.0	0.0022	2.3	0.0029	3.1	80	20
	0.241	0.0036	1.5	0.0052	2.1	0.0082	3.5	80	20
	0.481	0.0073	1.5	0.0113	2.3	0.0174	3.7	80	20
	1.92	0.029	1.5	0.047	2.4	0.070	3.7	80	20
	27.9	0.42	1.5	0.56	2.0	0.89	3.2	80	20
	77.4	1.45	1.8	1.83	2.3	2.88	3.8	80	20
	0.486	0.0070	1.4	0.0115	2.3	0.0165	3.4	80	20
	1.93	0.044	2.3	0.056	2.9	0.076	4.0	80	20
	55.5	1.13	2.0	1.45	2.6	2.16	3.9	80	20
5600****	0.037	0.0007	1.8	0.0019	5.0	0.0019	5.2	80	20
	0.093	0.0008	0.9	0.0021	2.2	0.0022	2.4	80	20
	0.236	0.0024	1.0	0.0047	2.0	0.0058	2.5	80	20
	0.471	0.0054	1.1	0.0108	2.3	0.0130	2.8	80	20
	1.90	0.021	1.1	0.047	2.5	0.055	2.9	80	20
	28.1	0.30	1.1	0.72	2.6	0.94	3.4	80	20
	75.7	1.33	1.7	2.30	3.0	3.02	4.0	80	20
	0.477	0.0045	0.9	0.0109	2.3	0.0137	2.9	80	20
	1.90	0.027	1.4	0.048	2.5	0.054	2.9	80	20
	55.2	0.99	1.8	1.53	2.8	1.90	3.5	80	20

* Within-run (repeatability). Between Duplicate precision averaged over all runs.

** Within-calibration. Total precision with weighted components of within-run, between-run, and between-day variation.

*** Within-lab. A measure of the effect of recalibration on total precision, calculated within reagent lot, using data from at least 4 calibrations.

**** Performance characteristics for the VITROS 5600 System are applicable to the VITROS XT 7600 System.

Specificity

Substances that do not Interfere

The VITROS B•R•A•H•M•S PCT test was evaluated for interference consistent with CLSI document EP07.[26] Of the compounds tested, none was found to cause a bias of >10% with the test at the concentrations indicated at nominal procalcitonin concentrations of 0.250 ng/mL and 2.00 ng/mL.

Compound	Concentration			Compound	Concentration	
Acetaminophen	200 µg/mL	1323 µmol/L		Hemoglobin	600 mg/dL	6.00 g/L
Acetylsalicylic Acid	65.2 mg/dL	3.62 mmol/L		Heparin	8000 IU/L	N/A
Alcohol	400 mg/dL	86.8 mmol/L		Ibuprofen	50.0 mg/dL	2.42 mmol/L
Azithromycin	1.15 mg/dL	14.6 µmol/L		Imipenem	1.18 mg/mL	3.72 mmol/L
Bilirubin, Conjugated	30.0 mg/dL	513 µmol/L		Levofloxacin	1.75 mg/dL	47.2 µmol/L
Bilirubin, Unconjugated	40.0 mg/dL	475 µmol/L		Loratadine	0.030 mg/dL	0.784 µmol/L
Biotin	3500 ng/mL	14.3 µmol/L		Nicotine	0.100 mg/dL	6.20 µmol/L
Caffeine	5.98 mg/dL	308 µmol/L		Noradrenaline	2.00 µg/mL	11.8 µmol/L
Celecoxib	24.0 mg/dL	629 µmol/L		Oxymetazoline HCl	0.009 mg/dL	0.334 µmol/L
Cetirizine HCl	0.360 mg/dL	7.80 µmol/L		Phenylephrine	0.018 mg/dL	1.10 µmol/L
Dextromethorphan	0.140 mg/dL	3.80 µmol/L		Prednisolone	0.300 mg/dL	8.31 µmol/L
Dobutamine	11.2 µg/mL	37.2 µmol/L		Rheumatoid Factor	2000 IU/mL	N/A
Dopamine	13.0 mg/dL	686 µmol/L		Salmeterol	60.0 ng/mL	0.099 µmol/L
Doxycycline	50.0 mg/L	104 µmol/L		Tiotropium	21.6 ng/mL	0.046 µmol/L
Epinephrine	0.180 mg/dL	8.20 µmol/L		Total Protein	11.7 g/dL	N/A
Fentanyl	10.0 mg/L	29.7 µmol/L		Triglyceride	2160 mg/dL	24.4 mmol/L
Furosemide	2.00 mg/dL	60.5 µmol/L		Vancomycin	2.60 mg/mL	1.75 mmol/L
HAMA (Human Anti-Mouse Antibody)	3600 ng/mL	0.024 µmol/L				

Cross-Reactivity

The cross-reactivity of the VITROS B•R•A•H•M•S PCT test was evaluated by adding the following substances to one human serum sample pool containing no procalcitonin.

Cross-Reactant	Cross Reactant Concentration	Mean Result of Control Pool	Mean Result of Cross-Reactant Pool	% Cross-Reactivity
	ng/mL	ng/mL	ng/mL	
Human Calcitonin	3.90 ng/mL	*	*	*
Human Katacalcin	25.6 ng/mL	*	*	*
Human α-CGRP	30.0 ng/mL	*	*	*
Human β-CGRP	30.0 ng/mL	*	*	*

* Not Detectable (ND). Concentration was below the measuring range of the test, 0.030–100 ng/mL.

The cross-reactivity of the VITROS B•R•A•H•M•S PCT test was evaluated by adding the following substances to one human serum sample pool containing procalcitonin at a concentration of 0.500 ng/mL.

Cross-Reactant	Cross Reactant Concentration	Mean Result of Control Pool	Mean Result of Cross-Reactant Pool	% Cross-Reactivity
	ng/mL	ng/mL	ng/mL	
Human Calcitonin	3.90 ng/mL	0.491	0.461	-0.8
Human Katacalcin	25.6 ng/mL	0.461	0.468	0.0
Human α-CGRP	30.0 ng/mL	0.491	0.460	-0.1
Human β-CGRP	30.0 ng/mL	0.491	0.467	-0.1

Cross-reactivity was expressed as the mean result obtained for the cross-reactant pool minus the mean result obtained for the control sample divided by the cross-reactant concentration in percentage term.

$$\% \text{ Cross-reactivity} = \frac{(\text{Mean Procalcitonin Result Cross-reactant Pool}) - (\text{Mean Procalcitonin Result Control Sample})}{\text{Concentration of Cross-Reactant}} \times 100$$

References

1. Vijayan AL, Maya V, Ravindran S, Saikant R, Lakshmi S, Kartik R and Manoj G. Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy. *Journal of Intensive Care.* (5):51: 1 – 7; 2017.
2. Markus B, Peter AW. The inflammatory response in sepsis. *Trends Immunol.* 34(3):129–36; 2013.
3. Lever A, Mackenzie I. Sepsis: definition, epidemiology, and diagnosis. *Br Med J.* 335:879–83; 2007.
4. Dunja M, Snezana B, Arsen U, Biljana D, Vladimir V. Use of presepsin and procalcitonin for prediction of SeptiFast results in critically ill patients. *J Crit Care.* 40:197–201; 2017.
5. Angus DC, Van der Poll T. Severe sepsis and septic shock. *N Engl J Med.* 369:840–51; 2013.
6. Moore LJ, McKinley BA, Turner K. The epidemiology of sepsis in general surgery patients. *J Trauma.* 70(3):672–80; 2011.
7. Taylor R, Jones A, Kelly S, et al. A review of the value of procalcitonin as a marker of infection. *Cureus*. Apr 10;9(4): e1148. doi:10.7759/cureus.1148; 2017.
8. Becker KL, Nylén ES, White JC, Müller B, Snider RH. Clinical review 167: Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. *J Clin Endocrinol Metab.* 89: 1512-1525; 2004.
9. Karzai W, Oberhoffer M, Meier-Hellmann A, Reinhart K. Procalcitonin -a new indicator of the systemic response to severe infections. *Infection*. 25: 329-334; 1997.
10. Shieraw B, Ebisa B, Kumar K, Boutin A, Frieri M. The Role of Procalcitonin as a Biomarker in Sepsis. *J Infect Dis Epidemiol.* 2:006; 2016.
11. Morgenthaler N.G, Struck J. et al. Detection of procalcitonin (PCT) in healthy controls and patients with local infection by a sensitive ILMA. *Clin Lab*. 48(5-6): 263-270; 2002.
12. Meisner M. Procalcitonin – Biochemistry and Clinical Diagnosis. *UNIMED Science*. ISBN 978-3-8374-1241-3; 2010.
13. Christ-Crain M, Jaccard-Stolz D. et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet.* 363(9409): 600-607; 2004.
14. Luyt C.E. et al. Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. *Am. J. Resp. Crit. Care Med*. 171(1) 48-53; 2005.
15. Brunkhorst F.M. et al. Kinetics of procalcitonin in iatrogenic sepsis. *Intensive Care Med.* 24: 888-892; 1998.
16. Schuetz P, Christ-Crain M. et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA*. 302(10): 1059-1066; 2009.
17. Bouadma L, Luyt C.E. et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet*. 375(9713): 463-474; 2010.
18. Schuetz P.et al. Serial Procalcitonin Predicts Mortality in Severe Sepsis Patients: Results From the Multicenter Procalcitonin MOnitoring SEpsis (MOSES) Study. *Crit. Care Med.* 45(5): 781–789; 2017.
19. Summers M. et al.: Luminogenic Reagent Using 3-Chloro 4-Hydroxy Acetanilide to Enhance Peroxidase/Luminol Chemiluminescence. *Clinical Chemistry*. 41. S73; 1995.
20. CLSI *Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Fourth Edition.* CLSI document M29-A4. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.
21. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.
22. Calam RR. Specimen Processing Separator Gels: An Update. *J Clin Immunoassay*. 11:86–90; 1988.
23. CLSI. *Collection of Diagnostic Venous Blood Specimens. 7th ed.* CLSI standard GP41. Wayne, PA: Clinical and Laboratory Standards Institute; 2017.
24. CLSI. *Tubes and Additives for Venous and Capillary Blood Specimen Collection; Approved Standard—Sixth Edition.* CLSI document GP39-A6. Wayne, PA: Clinical and Laboratory Standards Institute; 2010.
25. CLSI. *Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline - Fourth Edition*. CLSI guideline C24, Wayne, PA: Clinical and Laboratory Standards Institute; 2016.
26. CLSI. *Interference Testing in Clinical Chemistry. 3rd ed.* CLSI guideline EP07. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.
27. Levinson SS. The Nature of Heterophilic Antibodies and Their Role in Immunoassay Interference. *J Clin Immunoassay.* 15:108-115; 1992.
28. Müller B, Becker KL, Schächinger H, et al. Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. *Crit Care Med*. 28(4):977-983; 2000.
29. Harbarth S, Holeckova K, Froidevaux C, et al. Diagnostic value of procalcitonin, interleukin-6 and interleukin-8 in critically ill patients admitted with suspected sepsis. *Am J Respir Crit Care Med*. 164:396-402; 2001.
30. Brunkhorst FM, Wegscheider K, Forycki ZF, et al. Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock. *Intensive Care Med*. 26:148-152; 2000.
31. American College of Chest Physicians / Society of Critical Care Medicine Consensus Conference Committee. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med*. 20(6):864-874; 1992.
32. Schuetz P, Raad, I., and D.N. Amin, Using procalcitonin-guided algorithms to improve antimicrobial therapy in ICU patients with respiratory infections and sepsis. *Curr Opin Crit Care*. 19(5):453-60; 2013.

33. Schuetz P, et al. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. *Lancet Infect Dis*. 18: 95–107; 2018.
34. Reith H.B, et al. Procalcitonin in early detection of postoperative complications. *Dig Surg* . 15(3): 260-5; 1998.
35. Meisner M, et al. Postoperative plasma concentrations of procalcitonin after different types of surgery. *Intensive Care Med*. 24(7):680-4; 1998.
36. Chiesa C. et al. Reliability of procalcitonin concentrations for the diagnosis of sepsis in critically ill neonates. *Clinical Infectious Diseases*. 26:664-72; 1998.
37. Kruger S. and Welte T. Biomarkers in community-acquired pneumonia. *Expert Rev Respir Med*. 6(2):203-14; 2012.
38. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 26;404–413; 1934.
39. Rubin, DB. (1987). Multiple Imputation for Nonresponse in Surveys. New York: Wiley.
40. CLSI. *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition.* CLSI document EP17-A2. Wayne, PA: Clinical and Laboratory Standards Institute; 2012.
41. CLSI. *Measurement Procedure Comparison and Bias Estimation Using Patient Samples. 3rd ed.* CLSI Guideline EP09c. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.
42. Deming WE, Statistical Adjustment of Data. New York, NY: John Wiley and Sons; 1943.
43. CLSI. *Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition.* CLSI document EP05-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.

Glossary of Symbols

The following symbols may have been used in the labeling of this product.

Do Not Reuse	Upper Limit of Temperature	Range
Use by or Expiration Date (Year-Month-Day)	Lower Limit of Temperature	Range of Means
LOT Batch Code or Lot Number	Temperature Limitation	Midpoint
SN Serial Number	Consult Instructions for Use	Revised
REF Catalog Number or Product Code	Attention: The Instructions for Use (IFU) has been updated	Supersedes
Caution	S1 For use in Slide Supply 1	Σ Contains Sufficient for "n" Tests
Keep Dry (Protect from Moisture/Humidity)	S2 For use in Slide Supply 2	IVD *in vitro* Diagnostic Medical Device
Manufacturer	SI SI Units	Der Grüne Punkt (the Green Dot). Manufacturer follows certain packaging material waste disposal management regulations
Date of Manufacture	CONV Conventional Units	
EC REP Authorized Representative in the European Community	Value	σ Estimated within-lab SD
Corrosive	Flammable	Serious Health Hazards
Health Hazards	Acute Toxicity	Environmental or Aquatic Toxicity

Revision History

Date of Revision	Version	Description of Technical Changes*
2019-12-20	2.0	• Expected Values: Updated the table for clarity and updated the 95th percentile URL • Clinical Performance Characteristics: Qualitative comparison tables removed for clarity • Accuracy (Method Comparison): Table and plot diagram updated for supplemental data
2019-11-13	1.0	Initial version of Instructions for Use

* The change bars indicate the position of a technical amendment to the text with respect to the previous version of the document.

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_____ _____

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