VIDAS® B·R·A·H·M·S PCT™ (PCT)

Rx only IVD

INDICATIONS FOR USE

VIDAS® B·R·A·H·M·S PCT™ (PCT) is an automated test for use on the instruments of the VIDAS® family for the determination of human procalcitonin in human serum or plasma (lithium heparinate) using the ELFA (Enzyme-Linked Fluorescent Assay) technique.

Used in conjunction with other laboratory findings and clinical assessments, VIDAS® B•R•A•H•M•S PCT™ is intended for use as follows:

- to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock,
- to aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission, using a change in PCT level over time,
- to aid in decision making on antibiotic therapy for patients with suspected or confirmed lower respiratory tract infections (LRTI) – defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) – in an inpatient setting or an emergency department,
- to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

WARNINGS AND PRECAUTIONS – TEST INTERPRETATION

- VIDAS® B·R·A·H·M·S PCT™ (PCT) is not indicated to be used as a stand-alone diagnostic assay and should be used in conjunction with clinical signs and symptoms of infection and other diagnostic evidence.
- **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 ICU care at Day 4 and other covariates (e.g., age and SOFA score) are also significant predictors of 28-day cumulative mortality risk.
- Certain patient characteristics, such as severity of renal failure or insufficiency, may influence procalcitonin values and should be considered as potentially confounding clinical factors when interpreting PCT values.
- Increased PCT levels may be observed in severe illness such as polytrauma, burns, major surgery, prolonged or cardiogenic shock.
- PCT levels may not be elevated in patients infected by certain atypical pathogens, such as *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae.*
- The safety and performance of PCT-guided therapy for individuals younger than age 17 years, pregnant women, immunocompromised individuals or those on immunomodulatory agents, was not formally analyzed in the supportive clinical trials.

SUMMARY AND EXPLANATION OF THE TEST

Procalcitonin (PCT) is the prohormone of calcitonin. Whereas calcitonin is only produced in the C cells of the thyroid gland as a result of hormonal stimulus, PCT is secreted by different types of cells from numerous organs in response to proinflammatory stimulation, particularly bacterial infection (1). Depending on the clinical background, a PCT concentration above 0.25 ng/mL can indicate clinically relevant bacterial infection, requiring antibiotic treatment (2). At a PCT concentration > 0.5 ng/mL, in a patient with signs and symptoms of systemic inflammatory response (SIRS) should be considered a risk factor for the development of severe sepsis or septic shock (3, 4).

A timely diagnosis of severe sepsis and septic shock is vital since the early and specific treatment in these patients has been shown to improve outcomes (5). It is especially critical to identify, as soon as possible, those patients at increased risk of death. To that end, several methods of severity scoring have been developed for use in intensive care units including Acute Physiology and Chronic Health Evaluation (APACHE), APACHE II, APACHE III, Simplified Acute Physiology Score (SAPS), SAPS II, Sequential Organ Failure Assessment (SOFA) and Mortality Probability Model (MPM) (6).

Sepsis is an excessive reaction of the immune system and coagulation system to an infection (7). The diagnosis and monitoring of infected patients are major problems for physicians. Use of biomarker testing in conjunction with observation of clinical symptoms can help provide clarity and the quantitative, rapid and objective nature of these tests makes them useful for risk assessment (8). Risk assessment after initial diagnosis and treatment of severe sepsis and septic shock in ICU aids in distinguishing patients at low risk for adverse outcomes and who could be discharged from the ICU, from patients at high risk who may need care escalation.

It has been proven that PCT levels can increase quickly, specifically in patients with a serious bacterial infection. For laboratory diagnosis, PCT is therefore an important marker enabling differentiation between a bacterial infection and other causes of inflammatory reactions (2). Moreover, the resolution of the septic infection can be accompanied by a decrease in the PCT concentration which returns to normal with a half-life of 24 hours (9, 10), i.e. the continuous decline of PCT is indicative of effective source control measures and has been implicated in the safe de-escalation of antibiotic therapy (11, 12, 13).

Because of its role in the body's systemic response to infection and inflammation, in vitro diagnostic assays for the detection of PCT have been widely used for risk assessment (8). Studies have demonstrated that the kinetics of PCT change may be useful as an independent prognostic factor, with rapid PCT decreases being correlated with good outcomes (14). Conversely, static or increasing values have been correlated with adverse outcomes including mortality.
In patients with severe sepsis or septic shock PCT kinetics over the first 72 hours in ICU have been shown to provide independent prognostic information and better risk discrimination than the SAPS II clinical risk score (15). Additionally, multiple studies have shown that the kinetics of PCT over the first 3 to 6 days after onset of sepsis can distinguish between patients at high and low risk for poor outcomes including persistent bacteremia, superinfection and death (16-18). Thus, monitoring over the first 96 hours after diagnosis of sepsis can provide valuable information to the physician enabling more informed decisions about patient management and an improving or worsening condition.

Randomized clinical trials (RCTs) have demonstrated that the use of procalcitonin to guide the initiation and also the duration of antibiotic treatment in patients with LRTI significantly reduced antibiotic consumption across different LRTI diagnoses, which included community-acquired pneumonia, acute bronchitis and COPD exacerbations (12, 42). These randomized trials were conducted in different settings, including the Emergency Department (ED) (2), inpatients (2, 22, 25) and/or the ICU (11). In the ED, a cut-off concentration at 0.25 ng/mL was used to either withhold or stop antibiotics in LRTI patients (42, 43, 44).

The reduction of antibiotic consumption was clinically safe in this framework, as no higher rates of mortality or treatment failure were associated with a PCT-guided antibiotic therapy (42). The safe reduction of antibiotics use through PCT-guided therapy was confirmed in an observational quality surveillance study that considered consecutive LRTI patients, recruited without exclusion criteria, who were seen at an emergency department (43).

Similarly, in the case of sepsis, the third edition of the Surviving Sepsis Campaign (SSC) Guidelines suggests that procalcitonin can be used to assist clinicians in the discontinuation of empiric antibiotics when no evidence of infection is found (2C recommendation)(5). Randomized clinical trials have also demonstrated the value of using PCT to guide in the discontinuation of antibiotics in patients with sepsis. The Stop Antibiotics on Procalcitonin Guidance Study (SAPS) (13) showed a reduction in antibiotic duration days from 7 days in the standard-of-care group to 5 days in the Procalcitonin-guided group, and a lower 28-day mortality in the Procalcitonin guided group (19.6%) compared to the standard-of-care group (25.0%). Another large, prospective, randomized study (11) showed that procalcitonin-guided antibiotic treatment substantially lowers antibiotic exposure.

For patients in the procalcitonin group, there was an absolute difference of 2.7 days in the number of days without antibiotics by day 28 corresponding to a 23% relative reduction in antibiotic exposure. Another study involving surgical Intensive Care Unit patients (34), demonstrated the usefulness of PCT as a helpful tool to decide the duration of antibiotic treatment.

Hospitals with low baseline durations of antibiotic therapy may not observe the same magnitude in reduction in antibiotic use, and the utility of procalcitonin for existing antimicrobial stewardship programs should be considered.

Viral infections, allergies, autoimmune diseases and graft rejection do not lead to a significant increase in PCT (19).

PRINCIPLE OF THE PROCEDURE

The assay principle combines a one-step immunoassay sandwich method with a final fluorescent detection (ELFA).
The Solid Phase Receptacle (SPR®), serves as the solid phase as well as the pipetting device. Reagents for the assay are ready-to-use and pre-dispensed in the sealed reagent strips.
All of the assay steps are performed automatically by the instrument. The sample is transferred into the wells containing anti-procalcitonin antibodies labeled with alkaline phosphatase (conjugate). The sample/conjugate mixture is cycled in and out of the SPR® several times. This operation enables the antigen to bind with the immunoglobulins fixed to the interior wall of the SPR® and the conjugate to form a sandwich. Unbound compounds are eliminated during washing steps.
Two detection steps are performed successively. During each step, the substrate (4-Methyl-umbelliferyl phosphate) is cycled in and out of the SPR®. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product (4-Methyl-umbelliferone) the fluorescence of which is measured at 450 nm. The intensity of the fluorescence is proportional to the concentration of antigen present in the sample.
At the end of the assay, results are automatically calculated by the instrument in relation to two calibration curves corresponding to the two detection steps. A fluorescence threshold value determines the calibration curve to be used for each sample. The results are then printed out.

KIT COMPOSITION (60 TESTS):

60 PCT strips	STR	Ready-to-use.
60 PCT SPR®s 2 x 30	SPR®	Ready-to-use. Interior of SPR®s coated with mouse monoclonal anti-human procalcitonin immunoglobulins.
PCT controls C1 control 2 x 2 mL (lyophilized) C2 control 2 x 2 mL (lyophilized)	C1 C2	Reconstitute with 2 mL distilled water. Let stand for 5 - 10 minutes then mix. Stable after reconstitution for 8 hours at 2-8°C, or until the expiration date on the kit at - 25 ± 6°C. 5 freeze/thaw cycles are possible. TRIS NaCl buffer (pH 7.3) + recombinant human PCT + preservatives. MLE data indicate the confidence interval in ng/mL ("Control C1 Dose Value Range" or "Control C2 Dose Value Range").
PCT calibrators S1 calibrator 2 x 2 mL (lyophilized) S2 calibrator 2 x 2 mL (lyophilized)	S1 S2	Reconstitute with 2 mL distilled water. Let stand for 5 - 10 minutes then mix. Stable after reconstitution for 8 hours at 2-8°C, or until the expiration date on the kit at - 25 ± 6°C. 5 freeze/thaw cycles are possible. TRIS NaCl buffer (pH 7.3) + recombinant human PCT + preservatives. MLE data indicate the calibrator concentration in ng/mL ("Calibrator (S1) Dose Value" or "Calibrator (S2) Dose Value") and the confidence interval in "Relative Fluorescence Value ("Calibrator (S1) RFV Range" or "Calibrator (S2) RFV Range").
Specifications for the factory master data required to calibrate the test: • MLE data (Master Lot Entry) provided in the kit or • MLE barcodes printed on the box label.		
1 package insert provided in the kit or downloadable from www.biomerieux.com/techlib.		

The SPR®

The interior of the SPR® is coated during production with mouse monoclonal anti-procalcitonin immunoglobulins. Each SPR® is identified by the "PCT" code. Only remove the required number of SPR®s from the pouch and **carefully reseal the pouch after opening.**

The reagent strip

The strip consists of 10 wells covered with a labeled, foil seal. The label comprises a bar code which mainly indicates the assay code, kit lot number and expiration date. The foil of the first well is perforated to facilitate the introduction of the sample. The last well of each strip is a cuvette in which the fluorometric reading is performed. The wells in the center section of the strip contain the various reagents required for the assay.

Description of the PCT strip

Wells	Reagents
1	Sample well.
2 - 3 - 4	Empty wells.
5	Conjugate: alkaline phosphatase-labeled mouse monoclonal anti-human procalcitonin immunoglobulins + preservative (400 µL).
6 -7 - 8	TRIS NaCl Tween (pH 7.3) + preservative (600 µL).
9	Empty well.
10	Reading cuvette with substrate: 4-Methyl-umbelliferyl phosphate (0.6 mmol/L) + diethanolamine* (DEA*) (0.62 mol/L or 6.6%, pH 9.2) + 1g/L sodium azide (300 µL).

* Signal Word: **DANGER**

Hazard statement

H318: Causes serious eye damage.

Precautionary statement

P280: Wear protective gloves/protective clothing/eye protection/face protection.
P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

For further information, refer to the Safety Data Sheet.

MATERIAL REQUIRED BUT NOT PROVIDED

- Pipette with disposable tip to dispense 2 mL and 200 µL.
- Powderless, disposable gloves.
- For other specific materials, please refer to the Instrument Operator's Manual.
- Instruments of the VIDAS® family: VIDAS®, mini VIDAS® or VIDAS® 3.

WARNINGS AND PRECAUTIONS – PROCEDURE

- **For *in vitro* diagnostic use only.**
- **Caution: US Federal Law restricts this device to sale by or on the order of a licensed practitioner.**
- **For professional use only.**
- **This kit contains products of animal origin. Certified knowledge of the origin and/or sanitary state of the animals does not totally guarantee the absence of transmissible pathogenic agents. It is therefore recommended that these products be treated as potentially infectious and handled observing the usual safety precautions (do not ingest or inhale).**
- Do not use the SPR®s if the pouch is pierced.
- Do not use visibly deteriorated STRs (damaged foil or plastic).
- Do not use reagents after the expiration date indicated on the label.
- Do not mix reagents or disposables from different lots.
- Kit reagents contain 1 g/L sodium azide which can react with lead or copper plumbing to form explosive metal azides. If any liquid containing sodium azide is disposed of in the plumbing system, drains should be flushed with water to avoid build-up.
- The substrate (well 10) contains an irritant agent (6,6% diethanolamine). Refer to the hazard statements "H" and the precautionary statements "P" above.
- Spills should be wiped up thoroughly after treatment with liquid detergent and a solution of household bleach containing at least 0.5% sodium hypochlorite. See the Operator's Manual for cleaning spills on or in the instrument. Do not place solutions containing bleach in the autoclave.
- The instrument should be routinely cleaned and decontaminated. See the Operator's Manual for the appropriate procedures.

PROCEDURAL LIMITATIONS

- Deviations from the instructions for use in this package insert may yield erroneous results.
- **Plasma collected in EDTA tube should not be used** as EDTA causes a decrease in the values measured
- **For a given patient, the PCT assays must be performed on the same type of sample tube.**
- Use **powderless** gloves, as powder has been reported to cause false results for certain enzyme immunoassay tests.
- Interference may be encountered with certain samples containing antibodies directed against reagent components.
- The effect of interfering substances has only been evaluated for those listed in the labeling. Interference by substances other than those described in the Interference section below could lead to erroneous results.

STORAGE CONDITIONS

- Store the VIDAS® B·R·A·H·M·S PCT™ (PCT) kit at 2-8°C.
- **Do not freeze reagents, with the exception of calibrators and controls after reconstitution.**
- **Store all unused reagents at 2-8°C.**
- After opening the kit, check that the SPR® pouch is correctly sealed and undamaged. If not, do not use the SPR®s.
- **Carefully reseal the pouch with the desiccant inside after use to maintain stability of the SPR®s and return the complete kit to 2-8°C.**
- If stored according to the recommended conditions, all components are stable until the expiration date indicated on the label. Refer to the kit composition table for special storage conditions.

SPECIMENS

Specimen type and collection

Human serum or plasma (lithium heparinate).

Sample preparation

- Dry tubes: wait for samples to coagulate and **centrifuge** according to the tube manufacturer's recommendations to eliminate fibrin.
- Other tubes: follow the tube manufacturer's recommendations for use.
- Frozen-stored samples: after thawing, mix by vortex or inversion, and clarify by centrifuging

Note: Blood sampling tube results may vary from one manufacturer to another depending on the materials and additives use.

It is the responsibility of each laboratory to validate the type of sample tube used and to follow the manufacturer's recommendations for use.

Sample preparation

Follow the tube manufacturer's recommendations for use.

The pre-analytical step, including the preparation of blood samples, is an essential first step when performing laboratory testing and should be in accordance with Good Laboratory Practice.

For serum specimens, ensure that complete clot formation has taken place prior to centrifugation. Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting times.

Samples containing suspended fibrin particles or erythrocyte stroma should be centrifuged before testing. The presence of fibrin, red blood cells, or suspended particles can lead to erroneous results.

Sample stability

The sera or plasma separated from the clot can be stored at 2-8°C in stoppered tubes for up to 48 hours; if longer storage is required, freeze at -25 ± 6°C. Six-month storage of frozen samples does not affect the quality of results. Three freeze/thaw cycles were validated.

Special case for low sample volumes

Sample volumes between 50 µL and 200 µL can be tested after performing a manual dilution up to 1/4 (1 volume of test sample + 3 volumes of PCT negative sample or Serum Free reagent (ref. 66 581)) and no more than two hours after dilution.

Sample-related interferences

It is recommended not to use samples that are hemolyzed, lipemic or icteric and, if possible, to collect a new sample.
Refer to the section **PERFORMANCE - Study of drugs and other potentially interfering substances"** for the components or substances tested.

INSTRUCTIONS FOR USE

For complete instructions, see the User's Manual.

Reading VIDAS® Protocol Test Change (PTC) protocol data and MLE data

When using the assay for the first time:

With the external instrument barcode reader,

1. Scan the PTC barcode(s) at the end of the package insert or from www.biomerieux.com/techlib. This reading allows VIDAS® PTC protocol data to be transferred to the instrument software for its update.

2. Scan the MLE data on the box label.

Note: If the MLE data have been read before the VIDAS® PTC protocol, read the MLE data again.

When opening a new lot of reagents:

Enter the specifications (or factory master data) into the instrument using the master lot entry (MLE) data.
If this operation is not performed **before initiating the tests**, the instrument will not be able to print results.

Note: The master lot data need only be entered once for each lot.
It is possible to enter MLE data **manually or automatically** depending on the instrument (refer to the User's Manual).

Calibration

Calibration, using the **two calibrators** provided in the kit, must be performed each time a new lot of reagents is opened, after the master lot data (MLE) has been entered, **and then every 28 days**. This operation provides instrument-specific calibration curves and compensates for possible minor variations in assay signal throughout the shelf-life of the kit.
The calibrators, identified by S1 and S2, must be tested **in duplicate** (see VIDAS® Operator's Manual) in the same run. The calibration values must be within the set RFV ("Relative Fluorescence Value"). If this is not the case, **recalibrate using S1 and S2**.

Controls

Two controls are included in each VIDAS® B·R·A·H·M·S PCT™ (PCT) kit. These controls must be performed immediately after opening a new kit to ensure that reagent performance has not been altered. Each calibration must also be checked using these controls. The instrument will only be able to check these control values if they are identified by C1 and C2.

Results cannot be validated if the control values deviate from the expected values. Samples tested in the same run must be reassayed.

Note:

Control material should be tested in accordance with guidelines or requirements of local, state, and/or federal regulations or accrediting organizations.

Assay Procedure

1. **Remove the required reagents from the refrigerator.**
2. Use one "PCT" strip and one "PCT" SPR® for each sample, control or calibrator to be tested. **Make sure the storage pouch has been carefully resealed after the required SPR®s have been removed.**
3. The test is identified by the "PCT" code on the instrument. The calibrators must be identified by "S1" and by "S2", and tested **in duplicate**. If the controls need to be tested, they should be identified by C1 and C2 and tested singly.
4. Mix the calibrators and/or controls using a vortex-type mixer.
5. To obtain optimum results, refer to all the paragraphs in the **SPECIMENS** section.
6. Before pipetting, ensure that samples, calibrators and controls are free of bubbles.
7. **For this test, the calibrator, control, and sample test portion is 200 µL.**
8. Insert the "PCT" SPR®s and strips into the appropriate position on the instrument. Check to make sure the color labels with the assay code on the SPR®s and the Reagent Strips match.
9. **Initiate the assay immediately.** All the assay steps are performed automatically by the instrument.
10. Reclose the vials and return them to the required temperature after pipetting.
11. The assay will be completed within **approximately 20 minutes.** After the assay is completed, remove the SPR®s and strips from the instrument.
12. Dispose of the used SPR®s and strips into an appropriate recipient.

RESULTS AND INTERPRETATION

Once the assay is completed, results are analyzed automatically by the computer using two calibration curves which are stored by the instrument; the concentrations are expressed in ng/mL.
As no international standard is available, VIDAS® B·R·A·H·M·S PCT™ (PCT) is calibrated against an internal panel of human sera with known procalcitonin concentrations consistent with other B·R·A·H·M·S PCT assays. In case of patient follow-up, it is recommended to use the same PCT assay technique.
For PCT concentrations greater than 200 ng/mL, the measurement range can be extended up to 2000 ng/mL by one 1:10 dilution of the sample (1 volume of sample + 9 volumes of PCT negative sample or Serum Free reagent (ref. 66 581)). The final result should take into account the original dilution factor.

If the result obtained after dilution is below the measuring range for the test (0.05 ng/mL) then the VIDAS® instrument will report an "INVALID" result with the mention "over-diluted". The final result cannot be calculated and should be reported as **less than** (0.05 ng/mL x dilution factor). For example, a sample which is tested with a dilution at 1/4 should be reported as **less than** 0.2 ng/mL (0.2 = 0.05 x 4).

If the dilution factor has not been entered when the analysis has been requested (see Operator's Manual), multiply the result by the dilution factor to obtain the sample concentration.

Interpretation of test results should be made taking into consideration the patient's history, and the results of any other tests performed. For interpretation of specific indications of use, see 'Range of Expected Values' below.

RANGE OF EXPECTED VALUES
Interpretation of results for the different indications for use are as follows:

1. Risk assessment for progression to severe sepsis and septic shock

In agreement with the literature (3, 4), the results obtained with VIDAS® B·R·A·H·M·S PCT™ (PCT) during a study performed on patients admitted to intensive care units (refer to "Clinical performance" section) are as follows:

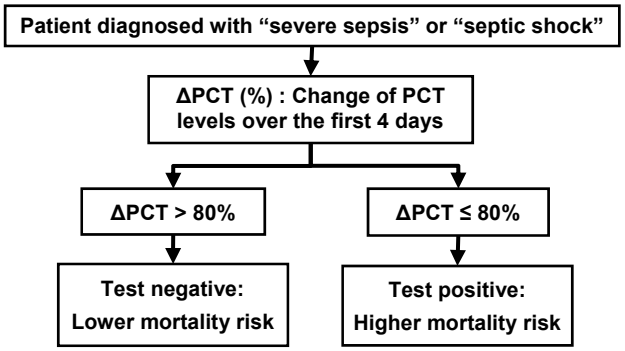
PCT Result	< 0.5 ng/mL	> 2 ng/mL
Indicates	Low risk of severe sepsis and/or septic shock	High risk of severe sepsis and/or septic shock
Note	Concentrations < 0.5 ng/mL do not exclude an infection, on account of localized infections (without systemic signs) which can be associated with such low concentrations, or a systemic infection in its initial stages (< 6 hours). Furthermore, increased procalcitonin can occur without infection. PCT concentrations between 0.5 and 2.0 ng/mL should be interpreted taking into account the patient's history. It is recommended to retest PCT within 6-24 hours if any concentrations < 2 ng/mL are obtained.	

2. Change of PCT over time

Procalcitonin (PCT) is a biomarker associated with the inflammatory response to bacterial infection that aids in the risk assessment of critically ill patients on their first day of Intensive Care Unit (ICU) admission for progression to severe sepsis and septic shock. The percent change in PCT level over time also aids in the prediction of cumulative 28-day mortality in patients with severe sepsis and septic shock.

- PCT levels on the first day of ICU admission above 2.0 ng/mL are associated with a higher risk for progression to severe sepsis and/or septic shock than PCT levels below 0.5 ng/mL.
- 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 (≤ 2.0 ng/mL or > 2.0 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 (refer to "Clinical performance" section) support the use of PCT determinations from the day severe sepsis or septic shock is first diagnosed (Day 0) or the day thereafter (Day 1) and the fourth day after diagnosis (Day 4) for the classification of patients into higher and lower risk for mortality within 28 days according to the workflow below:



ΔPCT ≤ 80% A decrease of PCT levels below or equal to 80% defines a positive ΔPCT 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.

ΔPCT Calculation In order to calculate the ΔPCT, use the following calculation.

$$\Delta PCT = \frac{PCT_{Day\,0} \square - PCT_{Day\,4} \square}{PCT_{Day\,0} \square} \times 100\%$$

If Day 0 result is not available, Day 1 result may be used.
If more than one PCT value is available on Day 0 (or Day 1), enter the highest value
If more than one PCT value is available on Day 4, enter the most recent value

A Change in Procalcitonin Calculator is available at **www.BRAHMS-PCT-Calculator.com**.

3. Decision making on antibiotic therapy for patients with suspected or confirmed LRTI

Initiation:

PCT Result	<0.10 ng/mL	0.10-0.25 ng/mL	0.26-0.50 ng/mL	>0.50 ng/mL
Interpretation	Antibiotic therapy strongly discouraged.	Antibiotic therapy discouraged.	Antibiotic therapy encouraged.	Antibiotic therapy strongly encouraged.
Follow-up	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 (41), based upon physician discretion taking into account patient's evolution and progress. Antibiotic therapy may be adjusted using the discontinuation table below:	

Discontinuation:

Antibiotic therapy may be discontinued if the $PCT_{Current}$ is ≤ 0.25 ng/mL or if the ΔPCT > 80%.

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

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

Antibiotic therapy may be continued based upon other clinical findings, such as apparent progression on chest x-ray or ongoing/increasing toxicity.

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

4. Decision making on antibiotic discontinuation for suspected or confirmed septic patients

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 (41), based upon physician discretion taking into account the patients' evolution and progress. Antibiotic therapy may be adjusted using the discontinuation table below:

Antibiotic therapy may be discontinued if the $PCT_{Current}$ is ≤ 0.50 ng/mL or if the ΔPCT > 80%.

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

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

Antibiotic therapy may be continued based upon other clinical findings, such as failure to control a local infection, or ongoing physiologic instability.

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

Suggestions for Laboratory Reports

It is suggested to report the numerical PCT values (individual or paired). For paired PCT values the report should also indicate if the ΔPCT(%) was ≤ 80% or > 80%. The laboratory report should include a reference or a link to the bioMérieux package insert for a guided interpretation of the test results.

PERFORMANCE

All tests were generated on a VIDAS® instrument except where noted. Studies performed using VIDAS® B·R·A·H·M·S PCT™ (PCT) gave the following results:

Measurement range

The VIDAS® B·R·A·H·M·S PCT™ (PCT) measurement range is 0.05-200 ng/mL.
For PCT concentrations greater than 200 ng/mL, the measurement range can be extended up to 2000 ng/mL by a 1:10 dilution of the sample.

Limits of detection and quantitation

The Limit of Blank (LoB), the Limit of Detection (LoD) and the Limit of Quantitation (LoQ) were determined on the VIDAS® and VIDAS®3 instruments according to the CLSI® EP17-A2 recommendations. The limits reported below apply for all the instruments of the VIDAS® family:

Limit of Blank (LoB)	0.01 ng/mL
Limit of Detection (LoD)	0.03 ng/mL
Limit of Quantitation (LoQ)	0.05 ng/mL

The LoQ was determined to be 0.05 ng/mL (with bias ≤ 10%, % CV ≤ 20% and total error ≤ 50%).

Hook effect

No hook effect was found up to procalcitonin concentrations of 2,600 ng/mL.

Normal values

These figures are given as a guide. It is recommended that each laboratory establishes its own reference values from a rigorously selected population.

A study was performed using the VIDAS® B·R·A·H·M·S PCT™ (PCT) test on serum samples from apparently healthy male (N=98) and female (N=102) subjects. The normal values corresponding to the 95th and 99th percentiles were respectively found at < 0.05 ng/mL and 0.09 ng/mL.

Precision

The study was performed according to the recommendations of CLSI® document EP5-A3. A panel of 11 human samples covering the measuring range were tested in duplicate in 2 runs per day, over 20 days using 3 VIDAS® and 3 VIDAS® 3 instruments (N=240 values for each sample) at 3 sites (one instrument per site). Two reagent lots were used: 10 days of tests and 6 calibrations were performed for each lot. The repeatability, between-day precision, within-laboratory precision and reproducibility/total precision (between-laboratory precision) were estimated for each sample and are reported in the following tables:

VIDAS®

Sample	N	Mean Concentration (ng/mL)	Repeatability		Between-Day Precision		Within-Laboratory Precision		Reproducibility / Total Precision	
			Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)
PP12	240	0.08	0.011	14.6%	0.012	15.9%	0.015	20.2%	0.015	20.2%
PP16	240	0.10	0.009	9.0%	0.011	10.4%	0.016	15.9%	0.016	15.9%
PS01	240	0.12	0.011	8.9%	0.013	10.8%	0.017	14.2%	0.017	14.2%
PS02	240	0.15	0.010	6.5%	0.014	8.9%	0.019	12.3%	0.019	12.3%
PP14	240	0.23	0.009	4.0%	0.011	4.9%	0.016	7.1%	0.016	7.1%
PS04	240	0.53	0.013	2.4%	0.021	4.0%	0.023	4.2%	0.023	4.2%
PS05	240	2.14	0.027	1.3%	0.063	3.0%	0.083	3.9%	0.083	3.9%
PS06	240	23.12	0.504	2.2%	0.882	3.8%	1.020	4.4%	1.020	4.4%
PS07	240	92.30	3.113	3.4%	5.972	6.5%	6.423	7.0%	6.423	7.0%
PS08	240	128.56	5.275	4.1%	9.562	7.4%	11.087	8.6%	11.087	8.6%
PS11	240	162.99	7.308	4.5%	11.377	7.0%	16.082	9.9%	16.082	9.9%

VIDAS® 3

Sample	N	Mean concentration (ng/mL)	Repeatability		Between-Day precision		Within-Laboratory precision		Reproducibility / Total precision	
			Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)
PP13	240	0.08	0.008	9.4%	0.009	10.4%	0.015	18.2%	0.015	18.2%
PP16	240	0.10	0.009	9.7%	0.010	10.9%	0.015	15.9%	0.015	15.9%
PS01	240	0.12	0.010	8.7%	0.011	9.4%	0.015	12.5%	0.015	12.5%
PS02	239	0.15	0.013	8.3%	0.014	9.3%	0.017	11.2%	0.017	11.2%
PP14	240	0.22	0.010	4.3%	0.011	4.9%	0.015	6.8%	0.015	6.8%
PS04	239	0.52	0.020	3.8%	0.024	4.6%	0.026	5.0%	0.032	6.1%
PS05	240	2.06	0.041	2.0%	0.073	3.5%	0.098	4.8%	0.102	5.0%
PS06	240	21.85	0.583	2.7%	0.814	3.7%	0.860	3.9%	0.946	4.3%
PS07	240	83.60	3.372	4.0%	4.445	5.3%	4.895	5.9%	5.785	6.9%
PS08	240	110.83	5.495	5.0%	7.091	6.4%	7.927	7.2%	8.525	7.7%
PS11	240	140.34	6.450	4.6%	10.611	7.6%	11.253	8.0%	12.596	9.0%

Specificity

The following compounds, tested at the concentrations indicated in the table, do not affect the VIDAS® B·R·A·H·M·S PCT™ (PCT) test.

Tested Compound	Tested Concentration
Human Calcitonin	60 ng/mL
Human Katacalcin	10 ng/mL
Human a-CGRP (*Calcitonin Gene Related Peptide)*	10 µg/mL
Human b-CGRP (*Calcitonin Gene Related Peptide)*	10 µg/mL

Study of drugs and other potentially interfering substances

Following the recommendations of CLSI® document EP7-A2, the potential interferences with the following drugs and potentially interfering substances were studied. No interference was observed at the concentration tested.

Tested Drug	Tested Concentration
Acetominophen (paracetamol)	20 mg/dL
Acetylsalicylic Acid	65.2 mg/dL
Alcohol	400 mg/dL
Amoxicillin	7.53 mg/dL
Ampicillin	5.31 mg/dL
Azithromycin	1.15 mg/dL
Beclometasone dipropionate	0.1 mg/dL
Caffeine	5.98 mg/dL
Cefotaxime	32.13 mg/dL
Ceftriaxone	93.7 mg/dL
Celecoxib	24 mg/dL
Cetirizine HCl	0.36 mg/dL
Cromolyn	2.4 mg/dL
Dextromethorphan	0.14 mg/dL
Dobutamine	0.15 mg/dL
Dopamine	0.11 mg/dL
Epinephrine (adrenaline)	0.18 mg/dL
Fluticasone	0.03 mg/dL

Tested Drug	Tested Concentration
Formoterol	0.0029 mg/dL
Furosemide	5.98 mg/dL
Heparin sodium	3000 UI/L
Ibuprofen	50 mg/dL
Imipenem	18 mg/dL
Levoflaxacin	1.75 mg/dL
Linezolid	48 mg/dL
Loratadine	0.03 mg/dL
Naproxen	50 mg/dL
Nicotine	0.1 mg/dL
Noradrenaline	0.00021 mg/dL
Oxymetazoline HCl	0.009 mg/dL
Phenylephrine	0.018 mg/dL
Prednisolone	0.3 mg/dL
Salmeterol	0.006 mg/dL
Theophylline	4 mg/dL
Tiotropium	0.0022 mg/dL
Vancomycin	10.25 mg/dL

Tested Substances	Tested Concentrations
Protein (albumin)	6.5 g/dL
Hemoglobin	600 mg/dL
Triglycerides	3000 mg/dL
Bilirubin	33 mg/dL

Linearity

The test linearity was studied on the VIDAS® and VIDAS® 3 instruments according to a procedure taken from the CLSI EP6-A guideline. The test is linear over the complete measurement range.

Concordance with the B·R·A·H·M·S PCT LIA method

A concordance study between VIDAS® B·R·A·H·M·S PCT™ (PCT) and B·R·A·H·M·S PCT LIA was performed using 204 samples with cut-off values at 0.5 ng/mL and 2 ng/mL.

VIDAS® B·R·A·H·M·S PCT™ (PCT)	**B·R·A·H·M·S PCT LIA**		
	≤ 0.5 ng/mL	**> 0.5 ng/mL**	**Total**
≤ 0.5 ng/mL	74	1	75
> 0.5 ng/mL	5	124	129
Total	79	125	204

VIDAS® B·R·A·H·M·S PCT™ (PCT)	**B·R·A·H·M·S PCT LIA**		
	≤ 2 ng/mL	**> 2 ng/mL**	**Total**
≤ 2 ng/mL	109	4	113
> 2 ng/mL	8	83	91
Total	117	87	204

The percentages of concordance between the 2 techniques for the cut-offs at 0.5 and 2 ng/mL are respectively 97.1% and 94.1%.

Clinical performance

1. Risk assessment for progression to severe sepsis and septic shock

A study performed on four (4) sites (2 in France and 2 in the USA) determined the clinical performance of the VIDAS® B·R·A·H·M·S PCT™ (PCT). This study included 232 patients (143 males and 89 females), who were consecutively admitted to the medical intensive care unit (MICU) on their first day of admission. The data represents first day admission testing.

Patients admitted for trauma, surgery, burns, or prolonged or severe cardiogenic shock were excluded from the study.

Based on criteria from the consensus conference of the American College of Chest Physicians/Society of Critical Care Medicine (5), patients were classified into 5 categories: no infection, SIRS (Systemic Inflammatory Response Syndrome), sepsis, severe sepsis and septic shock.

The number, range and mean age in each category were as follows:

- no infection : 35 patients aged between 22 and 92 years (mean 62.5 years)
- SIRS : 69 patients aged between 18 and 92 years (mean 58.7 years)
- sepsis : 24 patients aged between 21 and 86 years (mean 59.7 years)
- severe sepsis : 49 patients aged between 33 and 89 years (mean 69.1 years)
- septic shock : 55 patients aged between 33 and 88 years (mean 68.3 years)

PCT values for the groups of patients with no infection or SIRS or sepsis versus severe sepsis or septic shock with cut-offs at 0.5 ng/mL and 2.0 ng/mL are shown in the tables below:

- Results obtained with a cut-off at 0.5 ng/mL :

	No infection / SIRS / sepsis	Severe sepsis / septic shock	Total
PCT ≤ 0.5 ng/mL	74	18	92
PCT > 0.5 ng/mL	54	86	140
Total	128	104	232

- Results obtained with a cut-off at 2.0 ng/mL :

	No infection / SIRS / sepsis	Severe sepsis / septic shock	Total
PCT ≤ 2 ng/mL	98	37	135
PCT > 2 ng/mL	30	67	97
Total	128	104	232

2. Change of PCT over time

A study was conducted on a population of 858 adult patients recruited across 13 investigational sites in the US to assess the performance of VIDAS® B·R·A·H·M·S PCT™ (PCT) on VIDAS®3 and VIDAS® for the prediction of cumulative 28-day all-cause mortality.

In the per protocol population (598 patients) was comprised of 44% female and 56% male patients with a mean age of 64 years, diagnosed either with severe sepsis (51%) or septic shock (49%), presenting mainly with community acquired infections (91%) and less frequently with nosocomial infections (9%). All patients were admitted into ICU at some point during their hospital stay, 44% were still located in ICU at Day 4 of the study ("ICU" group), whereas 56% were at Day 4 already transferred to a location outside of the ICU ("non-ICU" group).

Demographics with patients' outcome and % mortality information are shown below:

Variable	Class	N*	Dead	Alive	% Mortality
Gender	**Female**	264	46	218	17.4%
	Male	334	55	279	16.5%
Age (years)	**≤ 30**	39	1	38	2.6%
	31-45	45	4	41	8.9%
	46-55	74	8	66	10.8%
	56-65	149	26	123	17.4%
	66-75	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%

*per protocol population

Cumulative 28-day all-cause mortality did not differ significantly for male vs. female patients ($\chi 2$ test p-value = 0.84).

Initial PCT levels at Day 0 with patients outcome and % mortality were as follows:

Variable	Class	VIDAS®3				VIDAS®			
		N	Dead	Alive	% Mortality	N	Dead	Alive	% Mortality
PCT on Day 0 (ng/mL)	**< 0.5**	101	17	84	16.8%	97	16	81	16.5%
	0.5-2.0	89	10	79	11.2%	92	10	82	10.9%
	> 2.0	373	70	303	18.8%	367	69	298	18.8%
	Unavailable*	35	4	31	11.4%	42	6	36	14.3%

* Unavailable patients results were either not available for testing (VIDAS®3 n = 24, VIDAS® n = 29), or were below assay measuring range of 0.05 ng/mL (VIDAS®3 n = 11, VIDAS® n = 13).

The study demonstrated that **for patients diagnosed with severe sepsis or septic shock, the 28-Day mortality was statistically significantly for patients with ΔPCT ≤ 80% compared to patients with ΔPCT > 80%**:

- Binary ΔPCT was significantly associated with 28-day cumulative mortality (Two-sided Fisher's Exact Test p-value 0.0003 and 0.002 for VIDAS®3 and VIDAS® respectively for ΔPCT based on Day 0 and p-value = 0.003 and 0.019 for VIDAS®3 and VIDAS® respectively for ΔPCT based on Day 1) and this association remained significant in each patient location subgroup, ICU vs. non ICU at Day 4 (for VIDAS®3 and VIDAS® respectively Cochran-Mantel-Haenszel Test p-value =0.006 and 0.016 using ΔPCT based on Day 0 and p-value = 0.023 and 0.073 using ΔPCT based on Day 1). The mortality in the group with ΔPCT ≤ 80 % was increased by a factor of 2.1 on VIDAS®3 and 1.9 on VIDAS® compared to the group with ΔPCT > 80% using ΔPCT based on Day 0 (factor 1.8 on VIDAS®3 and 1.6 on VIDAS® using ΔPCT based on Day 1). The observed mortality risk was generally higher in the ICU subgroup than in the non-ICU group (5.4 to 11.4% vs. 18.4 to 31.6%). In each subgroup, the mortality was even higher for patients with a ΔPCT ≤ 80% than for patients with a ΔPCT > 80%.

- Supplementary classification of patients based on the patient location on Day 4 and initial PCT level (< 2.0 vs. ≥ 2.0 ng/mL) at Day 0 (or Day 1) showed that in each patient location and initial PCT level subgroup, a PCT decrease ≤ 80% from Day 0 (or Day 1) to Day 4 constitutes a higher risk for mortality within 28 days compared to a higher PCT decline (> 80%). **For the prediction of absolute mortality risks, ICU disposition at Day 4 and initial PCT level at Day 0 (or Day 1) should be considered in addition to binary ΔPCT (≤ 80% or > 80%).**

Significantly reduced or increased mortality were observed by patient location and initial PCT level subgroups:

a) Patients still receiving ICU care on Day 4 or patients with initial PCT level > 2.0 ng/mL have a higher mortality risk from study Day 4 to the end of follow-up time (28 days) when the ΔPCT is ≤ 80% compared to when the ΔPCT is > 80%.

b) among patients who are still in the ICU on Day 4, patients with ΔPCT > 80% and an initial PCT level of ≤ 2.0 ng/mL on Day 0 have a particularly lower cumulative 28-day mortality risk compared to patients with an initial PCT level at Day 0 of > 2.0 ng/mL (2.2% vs. 20.3% on VIDAS®3; 1.8% vs. 21.4% on VIDAS®). In addition, regardless of the initial PCT level, patients in the ICU on Day 4 which have ΔPCT ≤ 80% (Day 0 to Day 4) have an even higher mortality risk (26.4% to 34.1% on VIDAS®3; 27.0% to 33.5% on VIDAS®).

c) even when they are no longer in the ICU on Day 4, patients with an initial PCT level > 2.0 ng/mL and with a ΔPCT ≤ 80% (Day 0 to Day 4) remain at high mortality risk (14.1% on VIDAS®3; 13.4% on VIDAS®).
Overall, a lower mortality risk was observed for patients discharged from the ICU before or on Day 4 with an initial PCT level ≤ 2.0 ng/mL than for patients with an initial PCT level of > 2.0 ng/mL (3.7% to 9.5% vs. 5.8% to 14.1% on VIDAS®3; 4.2% to 9.2% vs. 6.5% to 13.4% on VIDAS®).

The table below shows the 28-day cumulative mortality risk and prognostic accuracy by binary ΔPCT group (≤ 80% or > 80%), by the selection of either Day 0 or Day 1 for the ΔPCT calculation, by patient location at Day 4, and by initial PCT level.

	Mortality Risk by binary ΔPCT group and Prognostic Accuracy* by Patient Location on Day 4 and by initial PCT level						
	ΔPCT Interval	**Day 4 Patient Location**	**Initial PCT level**	**28 Day Mortality Risk**		**Prognostic Accuracy**	
				ΔPCT > 80% (95% CI)	**ΔPCT ≤ 80% (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
VIDAS® 3	**Day 0 to Day 4**	**ICU**	**All PCT levels**	**18.4%** (10.0-26.8%)	**31.3%** (24.5-38.1%)	**78.4%** (68.7-88.1%)	**35.7%** (28.7-42.7%)
			≤ 2.0 ng/mL	**2.2%** (0.0-15.1%)	**26.4%** (15.8-37.1%)	**98.8%** (91.7-100.0%)	**14.9%** (5.1-24.7%)
			> 2.0 ng/mL	**20.3%** (11.1-29.5%)	**34.1%** (25.3-42.9%)	**71.6%** (59.4-83.8%)	**44.6%** (36.0-53.3%)
		non ICU	**All PCT levels**	**5.4%** (1.8-9.1%)	**11.4%** (6.8-16.1%)	**71.7%** (55.0-88.3%)	**47.0%** (40.9-53.0%)
			≤ 2.0 ng/mL	**3.7%** (0.0-11.0%)	**9.5%** (3.9-15.1%)	**91.0%** (74.2-100.0%)	**21.2%** (13.2-29.1%)
			> 2.0 ng/mL	**5.8%** (1.6-10.0%)	**14.1%** (6.1-22.1%)	**59.6%** (36.4-82.8%)	**64.3%** (56.7-72.0%)
	Day 1 to Day 4	**ICU**	**All PCT levels**	**18.4%** (10.1-26.7%)	**31.6%** (24.7-38.5%)	**77.2%** (67.2-87.2%)	**37.7%** (30.6-44.7%)
			≤ 2.0 ng/mL	**12.6%** (0.0-34.0%)	**22.2%** (11.6-32.7%)	**90.6%** (74.1-100.0%)	**16.8%** (6.4-27.2%)
			> 2.0 ng/mL	**19.2%** (10.3-28.1%)	**36.8%** (27.8-45.7%)	**73.6%** (61.9-85.3%)	**46.7%** (38.0-55.3%)
		non ICU	**All PCT levels**	**7.0%** (2.8-11.2%)	**10.1%** (5.7-14.5%)	**63.8%** (45.8-81.8%)	**45.8%** (39.6-52.0%)
			≤ 2.0 ng/mL	**0.0%** (0.0-13.2*%)	**8.1%** (2.9-13.3%)	**100.0%** (66.4-100.0*%)	**20.7%** (12.9-28.4%)
			> 2.0 ng/mL	**8.5%** (3.5-13.5%)	**13.0%** (5.2-20.9%)	**48.1%** (25.7-70.5%)	**63.5%** (55.6-71.5%)
VIDAS®	**Day 0 to Day 4**	**ICU**	**All PCT levels**	**19.2%** (10.7-27.6%)	**31.0%** (24.2-37.8%)	**77.0%** (67.1-87.0%)	**36.1%** (29.1-43.1%)
			≤ 2.0 ng/mL	**1.8%** (0.0-12.8%)	**27.0%** (16.3-37.8%)	**98.9%** (92.4-100.0%)	**16.4%** (6.4-26.5%)
			> 2.0 ng/mL	**21.4%** (12.1-30.7%)	**33.5%** (24.6-42.3%)	**69.5%** (56.9-82.0%)	**44.8%** (36.1-53.5%)
		non ICU	**All PCT levels**	**6.1%** (2.2-10.0%)	**10.9%** (6.3-15.4%)	**68.2%** (51.0-85.4%)	**46.6%** (40.6-52.7%)
			≤ 2.0 ng/mL	**4.2%** (0.0-12.2%)	**9.2%** (3.8-14.7%)	**91.0%** (74.1-100.0%)	**19.0%** (11.4-26.6%)
			> 2.0 ng/mL	**6.5%** (2.1-10.8%)	**13.4%** (5.3-21.5%)	**53.9%** (30.3-77.6%)	**65.5%** (57.9-73.2%)
	Day 1 to Day 4	**ICU**	**All PCT levels**	**20.2%** (11.7-28.6%)	**30.8%** (23.9-37.7%)	**74.6%** (64.3-85.0%)	**37.5%** (30.4-44.5%)
			≤ 2.0 ng/mL	**2.2%** (0.0-14.2%)	**22.2%** (11.8-32.7%)	**98.2%** (88.5-100.0%)	**17.7%** (7.3-28.1%)
			> 2.0 ng/mL	**22.5%** (13.3-31.8%)	**35.6%** (26.6-44.5%)	**68.9%** (56.7-81.1%)	**46.2%** (37.5-54.8%)
		non ICU	**All PCT levels**	**7.3%** (2.9-11.6%)	**9.8%** (5.5-14.2%)	**63.6%** (45.5-81.7%)	**44.3%** (38.2-50.4%)
			≤ 2.0 ng/mL	**0.2%** (0.0-14.2%)	**6.9%** (2.1-11.8%)	**99.5%** (85.8-100.0%)	**19.0%** (11.5-26.4%)
			> 2.0 ng/mL	**8.7%** (3.5-13.8%)	**13.9%** (6.0-21.8%)	**50.8%** (28.9-72.6%)	**62.3%** (54.3-70.2%)

* Prognostic accuracy refers to how the binary ΔPCT can accurately predict mortality risk.

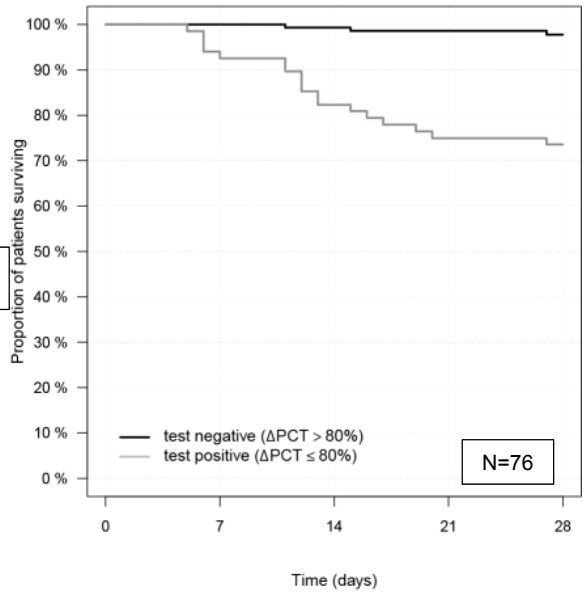
Time-to-event analysis is illustrated by the Kaplan-Meier survival probability curves below.

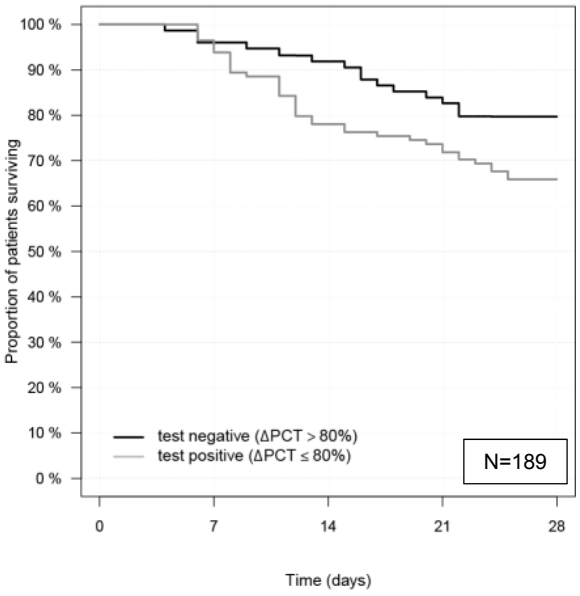
Survival probability until Day 28 for Patients still receiving ICU Care on Day 4

PCT ≤ 2.0 ng/mL at Day 0

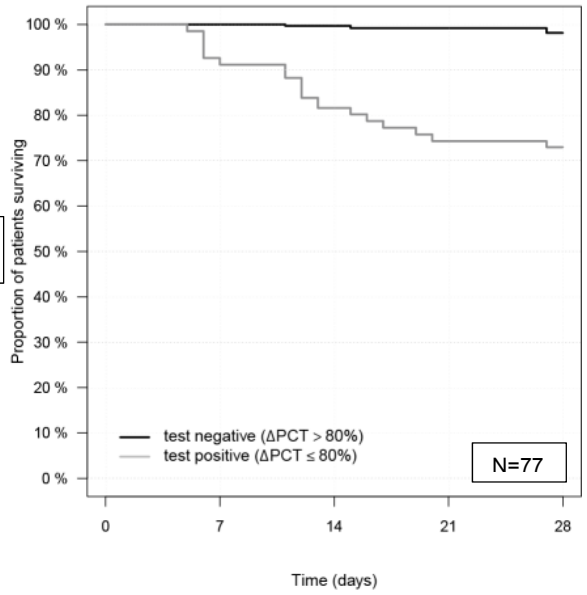
PCT > 2.0 ng/mL at Day 0

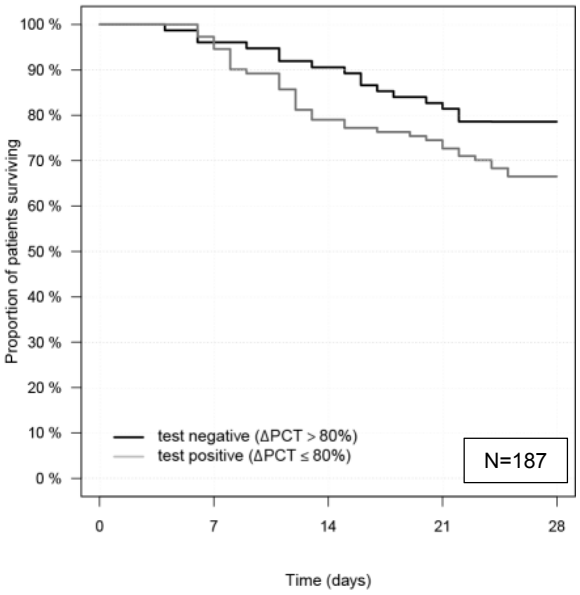
VIDAS®3





VIDAS®



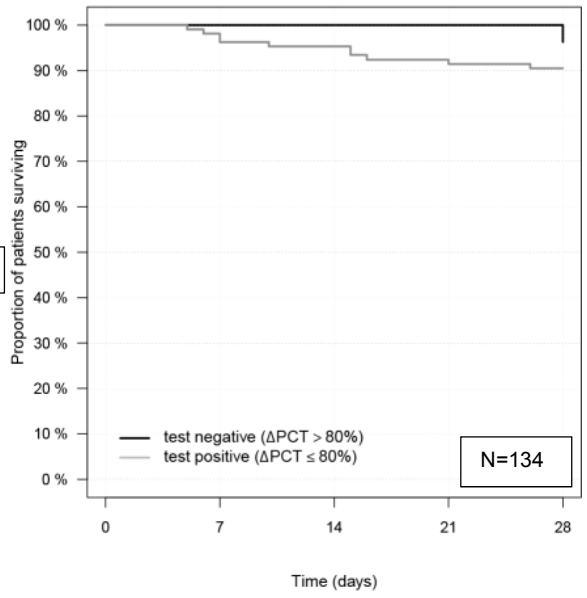


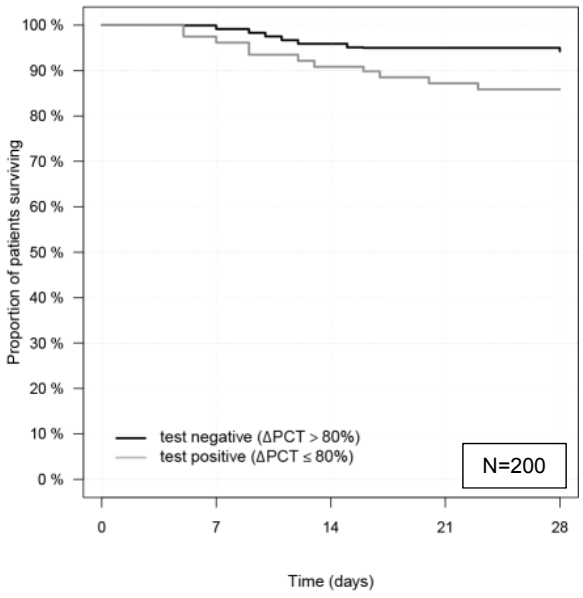
Survival probability until Day 28 for Patients without ICU Care on Day 4

PCT ≤ 2.0 ng/mL at Day 0

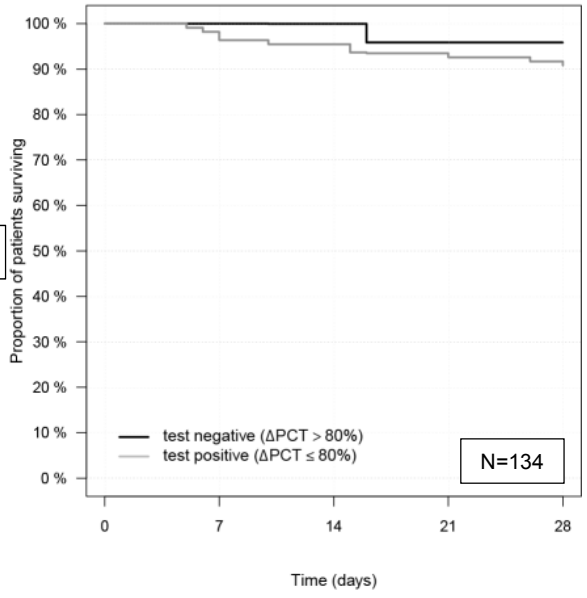
PCT > 2.0 ng/mL at Day 0

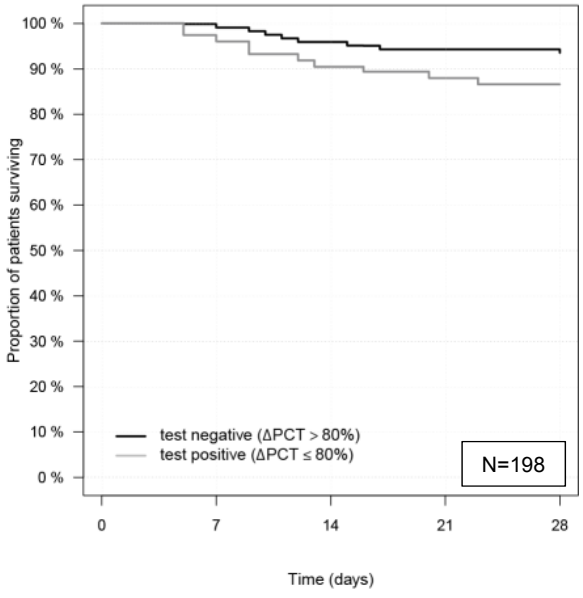
VIDAS®3





VIDAS®





Performance of binary ΔPCT from Day 0 to Day 4 for the prognosis of 28-day cumulative mortality risk was quantified by Cox proportional hazards regression. Hazard ratio of 2.27 and 2.05 were observed for VIDAS®3 and VIDAS® respectively: **patients with ΔPCT ≤ 80% have about a 2-fold higher 28-day mortality risk than patients with ΔPCT > 80%.**

In the table below, the relative mortality risk (univariate hazard ratios) are shown for binary ΔPCT, and for other clinical factors evaluated as separate predictors of mortality, for indication.

	Predictors	Comparison	Hazard Ratio	95% CI	p-Value
VIDAS® 3	**ΔPCT (Day 0 to Day 4)**	**≤ 80% vs. > 80%**	**2.27**	**1.41 - 3.63**	**0.0007**
	ΔPCT (Day 1 to Day 4)	≤ 80% vs. > 80%	1.96	1.24 - 3.11	0.004
	PCT on Day 0	>2 ng/mL vs. ≤ 2 ng/mL	1.38	0.89 - 2.14	0.149
VIDAS®	**ΔPCT (Day 0 to Day 4)**	**≤ 80% vs. > 80%**	**2.05**	**1.30 - 3.23**	**0.002**
	ΔPCT (Day 1 to Day 4)	≤ 80% vs. > 80%	1.74	1.11 - 2.73	0.015
	PCT on Day 0	>2 ng/mL vs. ≤ 2 ng/mL	1.39	0.89 - 2.15	0.145
	APACHE on Day 1	difference of 5 units	1.36	1.22 - 1.53	< 0.001
	Max 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
	ICU Care on Day 4	yes vs. no	3.45	2.24 - 5.31	< 0.001
	Biological Infection Type	gram positive vs. gram negative	0.83	0.48 - 1.45	0.522
	Biological Infection Type	Fungal vs. gram negative	2.44	0.87 - 6.84	0.09
	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
	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

The binary ΔPCT was shown to have an added-value related to other mortality predictors in the prognosis of the risk of 28-day mortality in patients diagnosed with severe sepsis or septic shock. The relative mortality risk (Hazard ratio) for binary ΔPCT and selected predictors (Patient location at Day 4, APACHE, max SOFA, Age) reported below were estimated with 95% confidence intervals using Cox multiple regression models adjusted for scores and other mortality predictors.

	Model		Hazard Ratio (95% Confidence Interval)				
			Binary Predictors		Continuous Predictors (HR per 1 SD)		
	ΔPCT Interval	Score + covariates*	ΔPCT (≤80% vs. >80%)	Patient Location at Day 4 (ICU vs. non ICU)	APACHE (1 SD = 8.13)	max SOFA (1 SD = 3.98)	Age (1 SD = 16.18)
VIDAS® 3	Day 0 to Day 4	**APACHE**	**2.11** (1.24-3.59)	2.59 (1.62-4.16)	1.23 (0.98-1.54)	---	1.61 (1.28-2.01)
		max SOFA	**1.81** (1.06-3.07)	1.68 (1.02-2.77)	---	1.93 (1.50-2.49)	1.69 (1.35-2.11)
	Day 1 to Day 4	**APACHE**	1.72 (1.05-2.82)	2.60 (1.62-4.16)	1.29 (1.03-1.61)	---	1.56 (1.25-1.95)
		max SOFA	1.60 (0.97-2.63)	1.70 (1.04-2.79)	---	1.99 (1.55-2.55)	1.65 (1.32-2.06)
VIDAS®	Day 0 to Day 4	**APACHE**	**1.82** (1.08-3.05)	2.60 (1.62-4.17)	1.24 (0.99-1.56)	---	1.59 (1.27-2.00)
		max SOFA	**1.59** (0.95-2.67)	1.68 (1.02-2.77)	---	1.96 (1.52-2.51)	1.69 (1.35-2.11)
	Day 1 to Day 4	**APACHE**	1.58 (0.97-2.57)	2.61 (1.63-4.17)	1.30 (1.04-1.63)	---	1.57 (1.25-1.96)
		max SOFA	1.42 (0.87-2.34)	1.72 (1.05-2.82)	---	1.99 (1.56-2.56)	1.67 (1.33-2.08)

* The models also included the following predictors considered as covariates (hazard ratio results not shown): Antibiotic Adequacy, Sepsis Severity, Biological Infection Type, Clinical Infection Type, Positive Blood Culture, PCT 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 (21).

Note: *For binary predictors, the risk estimate compares the hazards for the two binary results.*
For continuous predictors, the hazard ratio (HR) was calculated for one standard deviation (SD) change in the predictor.

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

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

A ΔPCT of 80% corresponds to a PCT ratio of 0.2 (i.e. PCT level at Day 4 is 5 times less than PCT level at Day 0, or Day 1). When ΔPCT is ≤ 80%, the PCT ratio is ≥ 0.2, 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 < 0.2 indicates a lower risk for mortality within 28 days. Validation of the VIDAS® B•R•A•H•M•S PCT™ (PCT) as an aid in predicting mortality was performed in a study population with an overall 28-day mortality of 22%.

On a continuous scale, the larger the PCT ratio, the higher the relative mortality risk is.
In the following table, the relative increase in mortality risk (hazard ratio) are reported for a patient with any given PCT ratio compared to a patient with a 2-fold lower PCT ratio. For comparison, other selected predictors (APACHE, max SOFA, Age, Patient location at Day 4) are indicated with corresponding equivalents in standard deviation (0.50 SD on VIDAS®3 and 0.51 SD on VIDAS® for Day 0 to Day 4; 0.69 SD on VIDAS®3 and 0.67 SD on VIDAS® for Day 1 to Day 4).

	Model*		**Hazard Ratio (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)**	**Max SOFA (SD equivalent)**	**Age (SD equivalent)**	**Patient Location at Day 4 (ICU vs. non ICU)**
VIDAS® 3	**Day 0 to Day 4**	APACHE	**1.28** (1.14-1.44)	1.07 (0.95-1.20)	---	1.28 (1.14-1.43)	2.50 (1.55-4.03)
		max SOFA	**1.21** (1.08-1.36)	---	1.34 (1.18-1.52)	1.31 (1.17-1.46)	1.68 (1.02-2.77)
	Day 1 to Day 4	APACHE	1.27 (1.09-1.48)	1.19 (1.02-1.39)	---	1.37 (1.18-1.60)	2.60 (1.62-4.17)
		max SOFA	1.21 (1.03-1.42)	---	1.58 (1.33-1.87)	1.43 (1.23-1.67)	1.75 (1.06-2.87)
VIDAS®	**Day 0 to Day 4**	APACHE	**1.29** (1.14-1.45)	1.08 (0.96-1.21)	---	1.28 (1.14-1.44)	2.49 (1.54-4.02)
		max SOFA	**1.22** (1.08-1.37)	---	1.35 (1.19-1.54)	1.31 (1.17-1.47)	1.68 (1.02-2.76)
	Day 1 to Day 4	APACHE	1.26 (1.08-1.46)	1.18 (1.02-1.37)	---	1.36 (1.17-1.58)	2.60 (1.62-4.17)
		max SOFA	1.19 (1.02-1.39)	---	1.56 (1.32-1.84)	1.42 (1.22-1.64)	1.75 (1.06-2.86)

*The models also included the following predictors considered as covariates (hazard ratio results not shown): Antibiotic Adequacy, Sepsis Severity, Biological Infection Type, Clinical Infection Type, Positive Blood Culture, PCT 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 (21).

3. Decision making on antibiotic therapy for patients with suspected or confirmed LRTI

Two systematic literature reviews were performed to produce both study and patient-level meta-analyses, which are studies that combine and contrast data from multiple sources to identify patterns among study results. The study-level meta-analysis used aggregate descriptive information extracted from publications, and the patient-level meta-analysis used aggregate patient-level data from the raw dataset of each study. Each meta-analysis used random-effects models and calculated point estimates, differences, odds ratios (OR), interquartile ranges (IQRs) and 95% confidence intervals as appropriate (see tables below). The endpoints evaluated were: proportion of subjects initiating antibiotics, duration of antibiotic therapy, exposure to antibiotics, length of hospital stay, mortality, and complications (patient level only).

For the study-level meta-analysis, initiation of antibiotics was expressed as an odds ratio (OR), while mortality was expressed as a risk ratio (RR). Duration of antibiotics, total exposure of antibiotics and length of hospital stay were expressed as a weighted mean difference. For the patient-level meta-analysis, duration of antibiotics, total exposure of antibiotics, and hospital length of stay were expressed as a difference while initiation of antibiotics, complications (death, hospitalization/ICU admission/rehospitalization, ARI-specific complications [empyema, meningitis], recurrent/worsening infection, or patients reporting ongoing respiratory infection symptoms) and 30-day mortality, were calculated as an odds ratio (OR). Adherence, defined as the proportion of patients in the PCT guided arms whose treatment decision was guided by PCT value alone, ranged in the study level meta-analysis from 59 to 91%, and in the patient level meta-analysis from 47 to 91%, when reported.

For both meta-analyses, duration was defined as length of time on antibiotics among patients who initiated treatment, and exposure was defined as length of time on antibiotics regardless of initiation. All studies included in the review were randomized controlled studies. Non-randomized studies were excluded.

The study-level meta-analysis encompassed 11 randomized control trials (RCTs) (2, 12, 22-30) which were published between 2004-2016, and included 4090 patients. The patient-level meta-analysis encompassed 13 RCTs (2, 11, 12, 23-28, 33, 35, 36, 39) which were published between 2004-2011, and included 3142 patients.

These meta-analyses concluded that PCT guided antibiotic therapy resulted in:

- 19.2% reduction in relative antibiotic initiation for all patients
- 38% reduction in overall antibiotic exposure (i.e. total days of antibiotic therapy) for inpatients
- 51% reduction in overall antibiotic exposure (i.e. total days of antibiotic therapy) for patients in emergency departments*
- 2.9 day reduction in antibiotic duration [1.25 day reduction in study-level]
- 3.6 day reduction in total antibiotic exposure [2.79 day reduction in study-level]
- No negative effects in regards to mortality, complications, or length of stay

*Patients who presented to the Emergency Department and other associated clinics, but were not admitted.

Additionally, a modified DOOR/RADAR analysis, in which patient outcomes were ranked by clinical severity, was conducted on the patient level data, and found that PCT-guided management had a statistically significant improvement in ranked patient outcomes compared to standard management.

The evaluated endpoints are segregated into study-level / patient-level and efficacy / safety categories below:

PCT guided antibiotic therapy (study-level meta-analysis results)

Parameter	# of RCTs Evaluated per Endpoint	# of Patients Evaluated*: Standard Care Therapy	# of Patients Evaluated*: PCT Guided Therapy	Results OR/RR or Difference (95% CI)
Overall	**11**	**2050**	**2040**	
Efficacy endpoints				
Initiation of antibiotics (OR)	10	1960	1952	0.26 (0.13, 0.52)
Antibiotic use (days)**	9	1854	1850	-2.15 (-3.30, -0.99)
Duration of antibiotics (days)	3	463	459	-1.25 (-2.92, 0.43)
Exposure of antibiotics (days)	5	1272	1267	-2.79 (-4.63, -0.96)
Safety endpoints				
Mortality (RR)***	9	1694	1684	0.94 (0.69, 1.28)
Hospital length of stay (days)	7	1319	1301	-0.15 (-0.60, 0.30)

*The # of patients evaluated indicates the total number of patients included in the evaluation.
**Antibiotic use is defined as the combination of the data from: antibiotic exposure (5 RCTs), antibiotic duration (3 RCTs) and 1 RCT whose definition (exposure or duration) was unclear.
***Mortality was defined per the individual RCT from which the data was extracted.

Demographics for the patients included in the patient-level meta-analysis are shown below:

Variable		Standard Care Therapy	PCT Guided Therapy
N		1606	1536
Age Median (IQR)		66 (49, 78)	66 (50, 79)
Gender	Male n (%)	862 (53.7%)	865 (56.3%)
	Female n (%)	744 (46.3%)	671 (43.7%)
Diagnosis	CAP n (%)	1028 (64.0%)	999 (65.0%)
	Bronchitis n (%)	282 (17.6%)	249 (16.2%)
	AECOPD n (%)	296 (18.4%)	288 (18.8%)
PCT concentration (ng/mL) at initiation Median (IQR)		0.21 (0.09, 1.04)	0.23 (0.10, 0.96)

Efficacy of PCT guided antibiotic therapy (patient-level meta-analysis results)

Parameter	Standard Care Therapy		PCT Guided Therapy		
	N included	N (%) or Days, median (IQR)	N included	N (%) or Days, median (IQR)	Adjusted OR or Difference (95%CI)
Overall	**1606**		**1536**		
Initiation of antibiotics	1606	1420 (88.4%)	1536	1096 (71.4%)	0.27 (0.22, 0.33)
Duration of antibiotics	1420	10 (7, 12)	1096	7 (4, 10)	-2.87 (-3.25, -2.48)
Total exposure of antibiotics	1606	9 (6, 12)	1536	5 (0, 8)	-3.60 (-3.97, -3.22)
Subgroup Analysis					
Subgroup by type of LRTI					
CAP (N)	**1028**		**999**		
Initiation of antibiotics	1028	1019 (99.1%)	999	898 (89.9%)	0.07 (0.03, 0.14)
Duration of antibiotics	1019	10 (8,14)	898	7 (5, 10)	-3.34 (-3.79, -2.88)
Total exposure of antibiotics	1028	10 (8,14)	999	6 (4,10)	-3.98 (-4.44, -3.52)
Bronchitis	**282**		**249**		
Initiation of antibiotics	282	185 (65.6%)	249	61 (24.5%)	0.15 (0.10, 0.23)
Duration of antibiotics	185	7 (5, 8)	61	7 (4,9)	-0.38 (-1.21, 0.46)
Total exposure of antibiotics	282	5 (0, 7)	249	0 (0, 0)	-3.06 (-3.69, -2.43)
AECOPD	**296**		**288**		
Initiation of antibiotics	296	216 (73.0%)	288	137 (47.6%)	0.32 (0.23, 0.46)
Duration of antibiotics	216	8 (6, 10)	137	6 (3, 9)	-1.58 (-2.33, -0.82)
Total exposure of antibiotics	296	7 (0, 10)	288	0 (0, 6)	-3.03 (-3.76, -2.30)
Subgroup by setting					
Inpatients	**1139**		**1106**		
Initiation of antibiotics	1139	1039 (91.2%)	1106	881 (79.7%)	0.35 (0.27, 0.46)
Duration of antibiotics	1039	10 (8, 14)	881	7 (4, 10)	-3.07 (-3.54, -2.60)
Total exposure of antibiotics	1139	10 (7, 13)	1106	6 (2, 9)	-3.73 (-4.20, -3.26)
Emergency Department*	**467**		**430**		
Initiation of antibiotics	467	381 (81.6%)	430	215 (50.0%)	0.13 (0.09, 0.19)
Duration of antibiotics	381	7 (6, 10)	215	6 (4, 8)	-1.68 (-2.21, -1.14)
Total exposure of antibiotics	467	7 (4, 9)	430	0.5 (0, 6)	-3.45 (-3.95, -2.95)
Subgroup by initial PCT level					
PCT <0.10 ng/mL	**416**		**388**		
Initiation of antibiotics	416	297 (71.4%)	388	134 (34.5%)	0.20 (0.15, 0.28)
Duration of antibiotics	297	7 (6, 10)	134	7 (4, 9)	-0.98 (-1.74, -0.21)
Total exposure of antibiotics	416	7 (0, 10)	388	0 (0, 4)	-3.45 (-4.07, -2.83)
PCT 0.10-0.25 ng/mL	**413**		**409**		
Initiation of antibiotics	413	361 (87.4%)	409	234 (57.2%)	0.16 (0.11, 0.23)
Duration of antibiotics	361	9 (7, 11)	234	5 (3, 7)	-3.25 (-3.96, -2.54)
Total exposure of antibiotics	413	8 (5, 10)	409	2 (0, 6)	-4.63 (-5.27, -3.99)
PCT 0.26-0.50 ng/mL	**215**		**217**		
Initiation of antibiotics	215	204 (94.9%)	217	212 (97.7%)	2.33 (0.79, 6.84)
Duration of antibiotics	204	10 (7, 12)	212	6 (4, 8)	-3.17 (-3.88, -2.45)
Total exposure of antibiotics	215	9 (6, 12)	217	5 (4, 8)	-2.82 (-3.58, -2.05)
PCT >0.50 ng/mL	**524**		**516**		
Initiation of antibiotics	524	521 (99.4%)	516	510 (98.8%)	0.46 (0.11, 1.89)
Duration of antibiotics	521	11 (8, 14)	510	8 (6, 11)	-3.19 (-3.87, -2.51)
Total exposure of antibiotics	524	11 (8, 14)	516	8 (5, 11)	-3.23 (-3.91, -2.54)
No baseline PCT value available	**38**		**6**		
Initiation of antibiotics	38	37 (97.4%)	6	6 (100%)	N/A**
Duration of antibiotics	37	13 (7, 17)	6	8.5 (4, 12)	-2.55 (-8.88, 3.78)
Total exposure of antibiotics	38	13 (7, 17)	6	8.5 (4, 12)	-2.03 (-8.44, 4.37)

*Patients who presented to the Emergency Department and associated clinics, but were not admitted.
**Effect could not be estimated.

Safety of PCT guided antibiotic therapy (patient-level meta-analysis results)

Parameter	Standard Care Therapy		PCT Guided Therapy		
	N included	N (%) or Days, median (IQR)	N included	N (%) or Days, median (IQR)	Adjusted OR or Difference (95%CI)
Overall	**1606**		**1536**		
30 days mortality	1606	119 (7.4%)	1536	103 (6.7%)	0.95 (0.77, 1.16)
Complications	1606	339 (21.1%)	1536	276 (18.0%)	0.82 (0.68, 0.99)
Hospital length of stay*	1583	6 (0, 13)	1508	7 (0, 12)	-0.18 (-0.85, 0.50)
Subgroup Analysis					
Subgroup by type of LRTI					
CAP	**1028**		**999**		
30 days mortality	1028	111 (10.8%)	999	92 (9.2%)	0.92 (0.74, 1.15)
Complications	1028	240 (23.4%)	999	190 (19.0%)	0.77 (0.62, 0.96)
Hospital length of stay	1005	7 (2, 14)	971	8 (2, 14)	-0.02 (-0.86, 0.82)
Bronchitis	**282**		**249**		
30 days mortality	282	0 (0.0%)	249	2 (0.8%)	N/A***
Complications	282	54 (19.2%)	249	51 (20.5%)	1.09 (0.70, 1.70)
Hospital length of stay	282	0 (0, 2)	249	0 (0, 2)	-0.18 (-0.88, 0.52)
AECOPD	**296**		**288**		
30 days mortality	296	8 (2.7%)	288	9 (3.1%)	1.15 (0.46, 2.89)
Complications	296	45 (15.2%)	288	35 (12.2%)	0.75 (0.46, 1.22)
Hospital length of stay	296	8 (3, 14)	288	8 (3, 13)	-0.84 (-2.94, 1.27)
Subgroup by setting					
Inpatients	**1139**		**1106**		
30 days mortality	1139	116 (10.2%)	1106	101 (9.1%)	0.95 (0.77, 1.17)
Complications	1139	254 (22.3%)	1106	199 (18.0%)	0.77 (0.62, 0.95)
Hospital length of stay	1116	10 (6, 15)	1078	9 (6, 15)	-0.45 (-1.37, 0.47)
Emergency Department**	**467**		**430**		
30 days mortality	467	3 (0.6%)	430	2 (0.5%)	1.11 (0.28, 4.45)
Complications	467	85 (18.2%)	430	77 (17.9%)	0.97 (0.68, 1.39)
Hospital length of stay	467	0 (0, 0)	430	0 (0, 0)	N/A***
Subgroup by initial PCT level					
PCT <0.10 ng/mL	**416**		**388**		
30 days mortality	416	5 (1.2%)	388	2 (0.5%)	0.43 (0.08, 2.19)
Complications	416	66 (15.9%)	388	58 (15.0%)	0.94 (0.63, 1.40)
Hospital length of stay	416	0 (0, 8)	388	0 (0, 8)	-0.78 (-2.24, 0.78)
PCT 0.10-0.25 ng/mL	**413**		**409**		
30 days mortality	413	23 (5.6%)	409	18 (4.4%)	0.78 (0.47, 1.30)
Complications	413	75 (18.2%)	409	57 (13.9%)	0.72 (0.49, 1.07)
Hospital length of stay	404	6 (1, 12)	397	7 (1, 11)	0.46 (-0.46, 1.38)
PCT 0.26-0.50 ng/mL	**215**		**217**		
30 days mortality	215	22 (10.2%)	217	15 (6.9%)	0.50 (0.29, 0.85)
Complications	215	46 (21.4%)	217	32 (14.7%)	0.60 (0.35, 1.03)
Hospital length of stay	209	7 (0, 13)	210	7 (0, 11)	-0.57 (-1.98, 0.83)
PCT >0.50 ng/mL	**524**		**516**		
30 days mortality	524	63 (12.0%)	516	68 (13.2%)	0.88 (0.69, 1.13)
Complications	524	146 (27.9%)	516	129 (25.0%)	0.79 (0.59, 1.06)
Hospital length of stay	516	8 (3, 15)	507	9 (4, 16)	0.03 (-1.23, 1.30)
No baseline PCT value available	**38**		**6**		
30 days mortality	38	6 (15.8%)	6	0 (0%)	N/A***
Complications	38	6 (15.8%)	6	0 (0%)	N/A***
Hospital length of stay	38	20 (10, 37)	6	20 (9, 22)	-7.04 (-20.08, 6.01)

*Length of stay patient data (n of 23 for standard care and n of 28 for PCT guided) was not collected for 2 RCTs (33, 36)
** Patients who presented to the Emergency Department and other associated clinics, but were not admitted.
***Effect could not be estimated.

4. Decision making on antibiotic discontinuation for septic patients

Two systematic literature reviews were performed along with study and patient-level meta-analyses, which are studies that combine and contrast data from multiple sources to identify patterns among study results. The study-level meta-analysis used aggregate descriptive information extracted from publications, and the patient-level meta-analysis used aggregate patient-level data from the raw dataset of each study. Each meta-analysis used random-effects models and calculated point estimates, differences, odds ratios (OR), interquartile ranges (IQRs) and 95% confidence intervals as appropriate (see tables below). The endpoints evaluated were: duration of antibiotic therapy (study level only), exposure to antibiotics (patient level only), length of ICU stay, length of hospital stay (patient level only), and mortality.

For the study-level meta-analysis, mortality was calculated as a risk ratio (RR), duration of antibiotics and ICU length of stay were expressed as weighted mean difference. For the patient level meta-analysis, total exposure of antibiotics, hospital length of stay and ICU length of stay were expressed as difference and 30-day mortality was calculated as an odds ratio (OR). Adherence, defined as the proportion of patients in the PCT guided arms whose treatment decision was guided by PCT value alone, ranged in the study level meta-analysis from 47 to 93%, and in the patient level meta-analysis from 47 to 91%, when reported.

For patient vs study both meta-analyses, duration was defined as length of time on antibiotics among patients who initiated treatment, and exposure was defined as length of time on antibiotics regardless of initiation. All studies included in the review were randomized controlled studies. Non-randomized controlled studies were excluded.

The study-level meta-analysis encompassed 10 RCTs (11, 13, 31-38) which were published between 2008-2016, and included 3489 patients. The patient-level meta-analysis encompassed 5 RCTs (11, 33, 35, 36, 40) which were published between 2008-2010, and included 598 patients.

These meta-analyses concluded that PCT guided antibiotic therapy resulted in:

- 1.5 day reduction in antibiotic duration
- 3.2 day reduction in total antibiotic exposure
- 23% reduction in overall antibiotic exposure (i.e. total days of antibiotic therapy)
- No negative effects in regards to mortality, hospital length of stay, or ICU length of stay.

The evaluated endpoints are segregated into study-level / patient-level and efficacy / safety categories below:

PCT guided antibiotic therapy (study-level meta-analysis results)

Parameter	# of RCTs Evaluated per endpoint	# of Patients Evaluated*: Standard Care Therapy	# of Patients Evaluated*: PCT Guided Therapy	Results (95% CI)
Overall	**10**	**1754**	**1735**	
Efficacy Endpoint				
Duration of antibiotics (days)	8	1470	1446	-1.49 (-2.27, -0.71)
Safety Endpoints				
Mortality (RR)**	10	1754	1735	0.90 (0.79, 1.03)
ICU length of stay (days)***	10	1751	1734	-0.84 (-2.52, 0.84)

*The # of patients evaluated indicates the total number of patients included in the evaluation.
**Mortality was defined per the individual RCT from which the data was extracted.
***Four patients evaluated for mortality were not evaluated for ICU length of stay.

Demographics for the patients included in the patient-level meta-analysis are shown below:

Variable		**Standard Care Therapy**	**PCT Guided Therapy**
N		311	287
Age Median (IQR)		65 (53, 75)	62 (50, 74)
Gender	Male n (%)	216 (69.5%)	208 (72.5%)
	Female n (%)	95 (30.5%)	79 (27.5%)
PCT concentration (ng/mL) at initiation Median (IQR)		1.20 (0.34, 4.74)	1.43 (0.39, 5.78)

Efficacy of PCT guided antibiotic therapy (patient-level meta-analysis results)

Parameter	**Standard Care Therapy**		**PCT Guided Therapy**		
	N	Days, median (IQR)	N	Days, median (IQR)	Difference (95%CI)
Overall					
Total exposure of antibiotics	311	12 (8, 18)	287	8 (5, 15)	-3.20 (-4.31, -2.08)
Subgroup Analysis by Initial PCT Level					
PCT ≤0.50 ng/mL					
Total exposure of antibiotics	77	10 (8, 18)	81	7 (4, 12)	-3.95 (-6.00, -1.90)
PCT >0.50 ng/mL					
Total exposure of antibiotics	159	14 (8, 20)	188	9 (6, 15)	-3.76 (-5.24, -2.28)
No Baseline PCT Value Available					
Total exposure of antibiotics	75	12 (7, 17)	18	11 (5, 23)	0.52 (-3.19, 4.23)

Safety of PCT guided antibiotic therapy (patient-level meta-analysis results)

Parameter	**Standard Care Therapy**		**PCT Guided Therapy**		
	N included	N (%) or Days, median (IQR)	N included	N (%) or Days, median (IQR)	Adjusted OR or Difference (95%CI)
Overall	**311**		**287**		
30 days mortality	311	74 (23.8%)	287	57 (19.9%)	0.87 (0.64, 1.18)
Hospital length of stay*	288	23 (13, 38)	259	21 (11, 37)	-1.35 (-4.44, 1.74)
ICU length of stay	311	12 (6, 22)	287	12 (6, 23)	1.05 (-1.25, 3.36)
Subgroup Analysis by Initial PCT Level					
PCT ≤0.50 ng/mL	**77**		**81**		
30 days mortality	77	24 (31.2%)	81	17 (21.0%)	0.70 (0.41, 1.20)
Hospital length of stay	62	24 (12, 38)	62	20 (10, 33)	-4.00 (-9.67, 1.97)
ICU length of stay	77	9 (6, 19)	81	11 (6, 21)	0.23 (-3.91, 4.37)
PCT >0.50 ng/mL	**159**		**188**		
30 days mortality	159	44 (27.7%)	188	40 (21.3%)	0.81 (0.56, 1.17)
Hospital length of stay	151	23 (13, 38)	179	21 (12, 39)	-1.05 (-5.18, 3.08)
ICU length of stay	159	13 (6, 23)	188	14 (6, 23)	0.64 (-2.51, 3.80)
No Baseline PCT Value Available	**75**		**18**		
30 days mortality	75	6 (8.0%)	18	0 (0%)	N/A**
Hospital length of stay	75	21 (12, 40)	18	21.5 (9, 30)	-1.59 (-10.81, 7.62)
ICU length of stay	75	12 (6, 23)	18	9 (5, 28)	2.36 (-4.81, 9.52)

*Length of stay patient data (n of 23 for standard care and n of 28 for PCT guided) was not collected for 2 RCTs (33, 36)
**Effect could not be estimated.

WASTE DISPOSAL

Dispose of used or unused reagents as well as any other contaminated disposable materials following procedures for infectious or potentially infectious products.
It is the responsibility of each laboratory to handle waste and effluents produced according to their nature and degree of hazardousness and to treat and dispose of them (or have them treated and disposed of) in accordance with federal, state and local regulations.

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INDEX OF SYMBOLS

Symbol	Meaning
REF	Catalog number
IVD	*In Vitro* Diagnostic Medical Device
Rx only	Caution: US Federal Law restricts this device to sale by or on the order of a licensed practitioner
	Temperature limit
	Use by date
LOT	Batch code
	Consult Instructions for Use
	Contains sufficient for <n> tests
UDI-DI	Unique Device Identification – Device Identifier
	Date of manufacture

LIMITED WARRANTY

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REVISION HISTORY

Change type categories :

N/A	Not applicable (First publication)
Correction	Correction of documentation anomalies
Technical change	Addition, revision and/or removal of information related to the product
Administrative	Implementation of non-technical changes noticeable to the user

Note: *Minor typographical, grammar, and formatting changes are not included in the revision history.*

Release date	Part Number	Change Type	Change Summary
2015/07	13975E	Administrative	INDEX OF SYMBOLS REVISION HISTORY
		Technical	KIT COMPOSITION (60 tests) MATERIALS AND DISPOSABLES REQUIRED BUT NOT PROVIDED, WARNINGS AND PRECAUTIONS, INSTRUCTIONS FOR USE
2016/02	13975F	Administrative	REVISION HISTORY
		Technical change	RESULTS AND INTERPRETATION
2016/06	13975G	Administrative	REVISION HISTORY
		Technical change	INTENDED USE SUMMARY AND EXPLANATION OF THE TEST MATERIAL REQUIRED BUT NOT PROVIDED SPECIMENS INSTRUCTIONS FOR USE RESULTS AND INTERPRETATION RANGE OF EXPECTED VALUES PERFORMANCE LITERATURE REFERENCES LIMITED WARRANTY
2017/02	13975H	Technical change	INTENDED USE / INDICATIONS FOR USE WARNINGS AND PRECAUTIONS SUMMARY AND EXPLANATION OF THE TEST PROCEDURAL LIMITATIONS SPECIMENS RANGE OF EXPECTED VALUES PERFORMANCE LITERATURE REFERENCES

Reagent developed in collaboration with B·R·A·H·M·S.

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